The American Journal of Cardiology®

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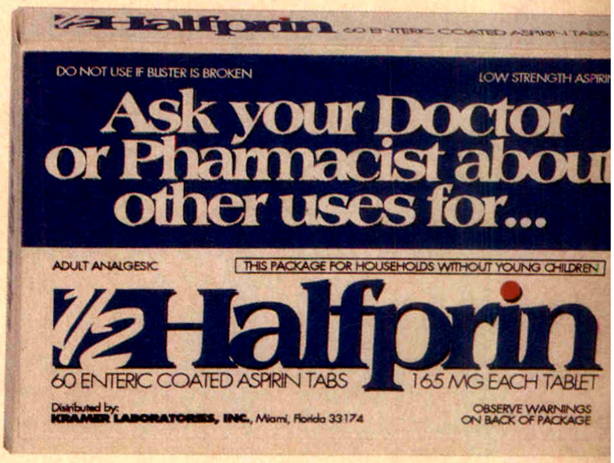
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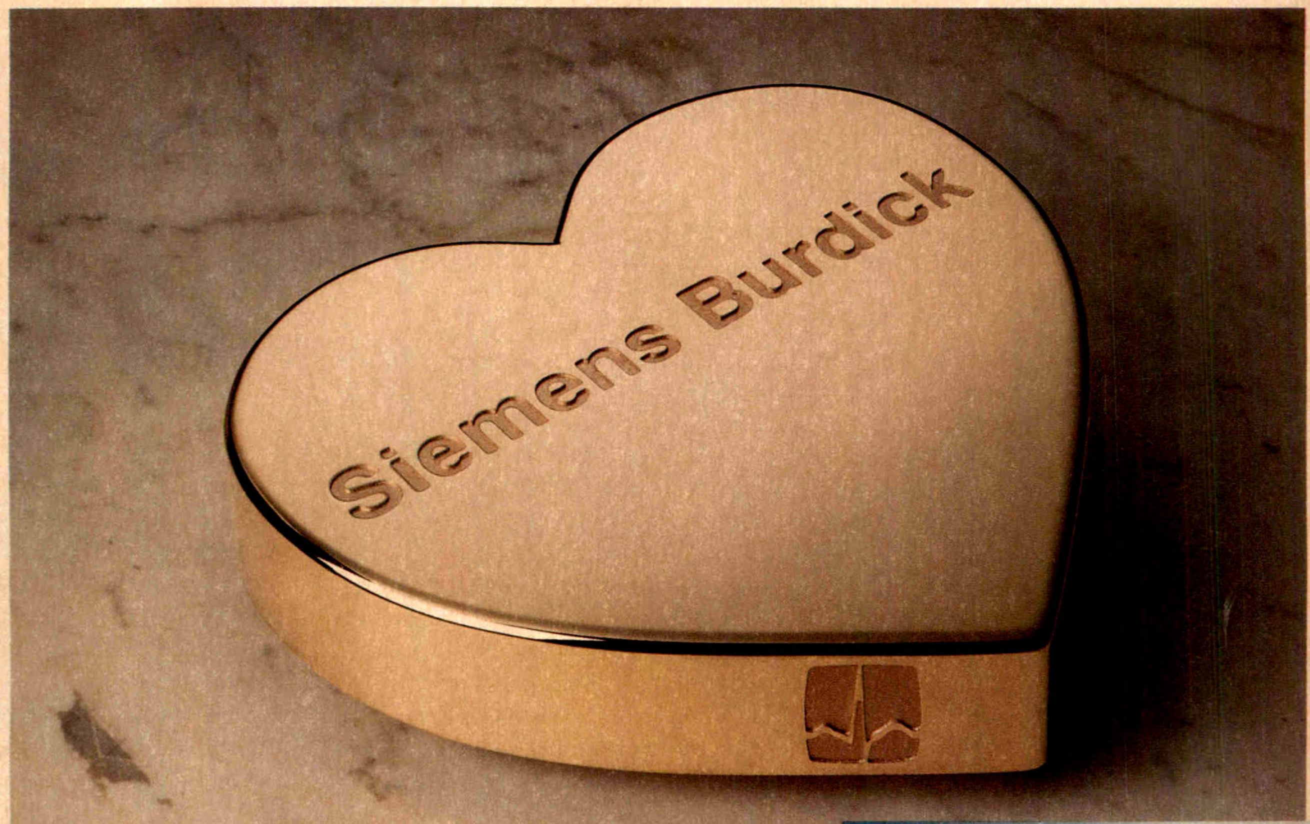

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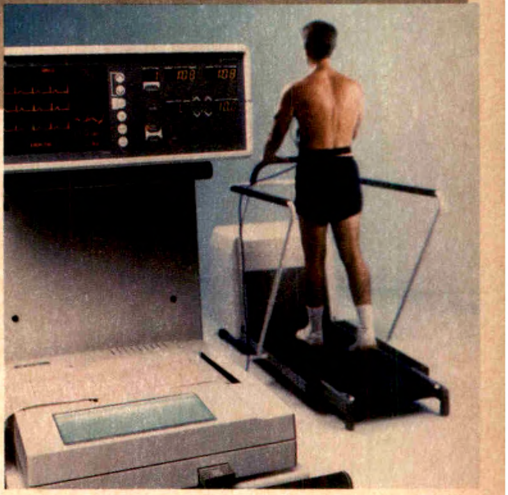

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CORONARY ARTERY DISEASE

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Enhancement of the Efficacy of Isosorbide Dinitrate by Captopril in Stable Angina Pectoris

Vladimir I. Metelitsa, Sergey Yu. Martsevich, Marina P. Kozyreva, and Irina D. Slastnikova

The possibility of interaction between isosorbide dinitrate (ISDN) and the angiotensin-converting enzyme inhibitor captopril was studied in 14 patients with stable angina pectoris. In each patient the antianginal and anti-ischemic effects of placebo, captopril (50 to 100 mg), ISDN (10 mg) and ISDN (10 mg) plus captopril (50 to 100 mg) was assessed by means of symptom-limited exercise treadmill tests performed before and 1, 2, 3 and 6 hours after single-dose administration. Captopril's antianginal and anti-ischemic effects were not significantly different from those of placebo. Combined administration of ISDN and captopril produced significantly more marked antianginal and anti-ischemic effects than did either drug alone. The most pronounced potentiation of ISDN efficacy after the addition of captopril was observed in 6 patients who had poor response to ISDN alone. It is concluded that captopril can potentiate the efficacy of nitrates, especially in patients who do not respond to their conventional doses.

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Identifying Coronary Artery Disease in Women by Heart Rate Adjustment of ST-Segment Depression and Improved Performance of Linear Regression Over Simple Averaging Method with Comparison to Standard Criteria

Peter M. Okin and Paul Kligfield

To assess the effect of gender on relative test performance of the ST-segment/heart rate (ST/HR) slope, the simple ST/HR index, and the rate-recovery loop for the identification of coronary artery disease (CAD), the exercise electrocardiograms of 254 patients with known or suspected CAD and of 150 clinically normal subjects were analyzed using an ST/HR slope partition of 2.40 μV/beat/min and an ST/HR index partition of 1.60 μV/beat/min. Specificity of each method was comparable in men and women: ST/HR slope 98% (118 of 121) vs 97% (28 of 29), ST/HR index 97% (117 of 121) vs 97% (28 of 29), and rate–recovery loop 96% (116 of 121) vs 93% (27 of 29). In contrast, although there was no difference in sensitivity of the ST/HR slope (95% [177 of 187] vs 93% [62

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of 67]; p = not significant [NS]) or rate–recovery loop (90% [168 of 187] vs 87% [58 of 67]; p = NS) between men and women, an ST/HR index partition of 1.60 was significantly less sensitive for CAD in women than in men (82% [55 of 67] vs 93% [173 of 187]; $p < 0.05$). Thus, among women sensitivity of the simple ST/HR index was significantly lower than that of the ST/HR slope for CAD (82 vs 93%; $p < 0.05$), but there was no significant difference in test performance of these 2 methods in men (93 vs 95%; p = NS). These findings support use of the more complex ST/HR slope method for the detection of CAD in women.

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Usefulness of Exercise-Induced ST-Segment Depression in the Inferior Leads During Exercise Testing as a Marker for Coronary Artery Disease

Cres P. Miranda, James Liu, Andras Kadar, Andras Janosi, Jeffrey Froning, Kenneth G. Lehmann, and Victor F. Froelicher

A retrospective analysis was performed of 173 men without prior myocardial infarction (108 in a training population and 65 in a second validation cohort) who underwent both exercise testing and coronary angiography to compare the diagnostic accuracy of precordial lead V_5 and limb lead II. The sensitivity and specificity of lead II did not reach statistical significance as a marker for coronary disease at a single cut point ($p = 0.13$) and at multiple cut points by receiver-operating characteristic curve analysis (area = 0.582; $p = 0.07$), whereas those of lead V_5 did on both counts ($p \leq 0.001$). Therefore, in patients with normal electrocardiograms, exercise-induced ST-segment depression in lead V_5 is an excellent marker for coronary disease and monitoring inferior lead II adds little independent diagnostic information.

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Comparison of One-, Six- and 24-Hour Ambulatory Electrocardiographic Monitoring for Ventricular Arrhythmia as a Predictor of Mortality in Survivors of Acute Myocardial Infarction

Stuart J. Connolly, and John A. Cairns, on behalf of the CAMIAT Pilot Study Group

One-, 6- and 24-hour electrocardiograms were compared for prediction of 1-year mortality in 560 surviving patients of acute myocardial infarction. Regression modeling of survival times showed all 3 recording durations to be good univariate predictors of survival. After the 1-hour data were accounted for by the model, neither the 6- nor 24-hour data contained statistically significant residual explanatory power for prediction of 1-year mortality. Increasing the duration of recording increased sensitivity at a cost of reduced specificity. The positive and negative predictive values of the 3 recording durations were virtually identical. There appears to be no benefit to recording durations >1 hour for mortality prediction after myocardial infarction.

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Clinical Angiographic and Histologic Correlates of Ectasia After Directional Coronary Atherectomy

Nicoletta B. De Cesare, Jeffrey J. Popma, David R. Holmes, Jr., Ronald J. Dick, Patrick L. Whitlow, Spencer B. King, Cass A. Pinkerton, Dean J. Kereiakes, Eric J. Topol, Christian C. Haudenschild, and Stephen G. Ellis

Directional coronary atherectomy can cause ectasia (final area stenosis <0%), due presumably to an excision deeper than the angiographically "normal" arterial lumen. In a multicenter series, ectasia after atherectomy occurred in 50 of 382 lesions (13%). The development of ectasia was associated with lesions within the circumflex coronary artery, with complex, probably thrombus-containing lesions, and with larger device:artery ratios. Histologic analysis demonstrated normal vessel wall components in all patients with angiographic ectasia. Restenosis, defined as a follow-up percent area stenosis ≥75%, was present in 50% of patients without procedural ectasia and in 70% of patients with marked ectasia (residual area stenosis <−20%). It is concluded that excision beyond the normal arterial lumen may occur after directional coronary atherectomy, related, in part, to angiographic and procedural features noted at the time of atherectomy. Restenosis tends to be higher in patients with marked ectasia after coronary atherectomy.

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Pulmonary Thallium-201 Uptake Following Dipyridamole-Exercise Combination Compared with Single Modality Stress Testing

Gilbert A. Hurwitz, J. Paul O'Donoghue, John E. Powe, Denis R. Gravelle, A. Craig MacDonald, and Keith J. C. Finnie

The combination of intravenous dipyridamole and symptom-limited exercise may have an advantage as a stress modality in conjunction with myocardial perfusion imaging. In a series of 400 patients with defined coronary artery anatomy, exercise alone was selected (n = 130) only where limiting physical and drug factors were absent; otherwise, dipyridamole was administered (n = 270) followed where possible by a significant level of exercise. Pulmonary uptake of thallium-201 on post-stress images was strongly related, whatever the test mode, to a score based on the location and number of severe (≥90%) coronary stenoses. Multiple regression analysis and receiver-operating curves suggested that increased pulmonary uptake tended to be seen more frequently when combined stress was used, compared with tests performed concurrently with either single modality. These data support a more widespread use of pharmacologic stress in myocardial imaging.

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Survey of Practicing Cardiologists in Maryland on Their Choice of Thrombolytic Therapy for Acute Myocardial Infarction

Gary D. Plotnick, Andrew A. Ziskind, and Robert A. Vogel

In November 1990, we surveyed 160 practicing community cardiologists in the state of Maryland and 20 academic cardiologists at the University of Maryland Medical Center to determine each clinician's choice of aggres-

sive versus nonaggressive therapy for various scenarios of acute myocardial infarction. Community cardiologists preferred tissue plasminogen activator and favored less aggressive therapy for early inferior acute myocardial infarction, while university cardiologists preferred streptokinase and were more aggressive. The survey was repeated in late April 1991. Despite increased use of streptokinase by community cardiologists, tissue plasminogen activator remained preferred over streptokinase.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

331

Survey of Cardiac Pacing in the United States in 1989

Alan D. Bernstein and Victor Parsonnet

A survey of physicians who implant permanent cardiac pacemakers was conducted to identify practice patterns related to frequency of pacemaker implantation, hospital and implantation-facility characteristics, indications for pacing and for pulse generator replacement, preferences regarding device types, pacing modes, follow-up methods and frequency, and type and freqency of pacing-related complications. Implanters' opinions were solicited regarding such issues as the importance of various device features and capabilities, the role of the pacemaker manufacturer's sales representative, the appropriateness of practice guidelines, and the efficacy of quality-assurance measures. In 1989, 89,445 primary pacemaker implantations and 21,055 pulse generator replacements were performed by approximately 7,819 physicians at about 3,400 U.S. centers. Dual-chamber and adaptive-rate pacemakers accounted for 32 and 40%, respectively, of primary implants.

339

Role of Sympathovagal Interaction in Diurnal Variation of QT Interval

Yuji Murakawa, Hiroshi Inoue, Akira Nozaki, and Tsuneaki Sugimoto

The role of sympathovagal interaction in the diurnal variation of QT interval was studied in 23 healthy subjects, 18 patients with coronary artery disease, and 15 patients with diabetes mellitus. The QT interval at a heart rate of 60 beats/min (QT60) was regressively determined for each of the day and night periods. Sympathetic and parasympathetic activities were assessed by the low- and high-frequency components of the power spectrum of heart rate variability, respectively. When the data from the 3 subject groups were pooled, the diurnal change in QT60 was correlated with that in sympathovagal balance estimated by the ratio between high-frequency component and the sum of low- and high-frequency components. Low-frequency component in the day alone was also related with the diurnal change in QT60. Thus, although variation of sympathovagal balance was responsible for the diurnal QT change, the enhanced sympathetic activity in the day was a major determinant of this phenomenon.

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unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazeprilat can be removed from the body by dialysis, but this intervention should rarely, if ever, be required.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m^2 (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg.

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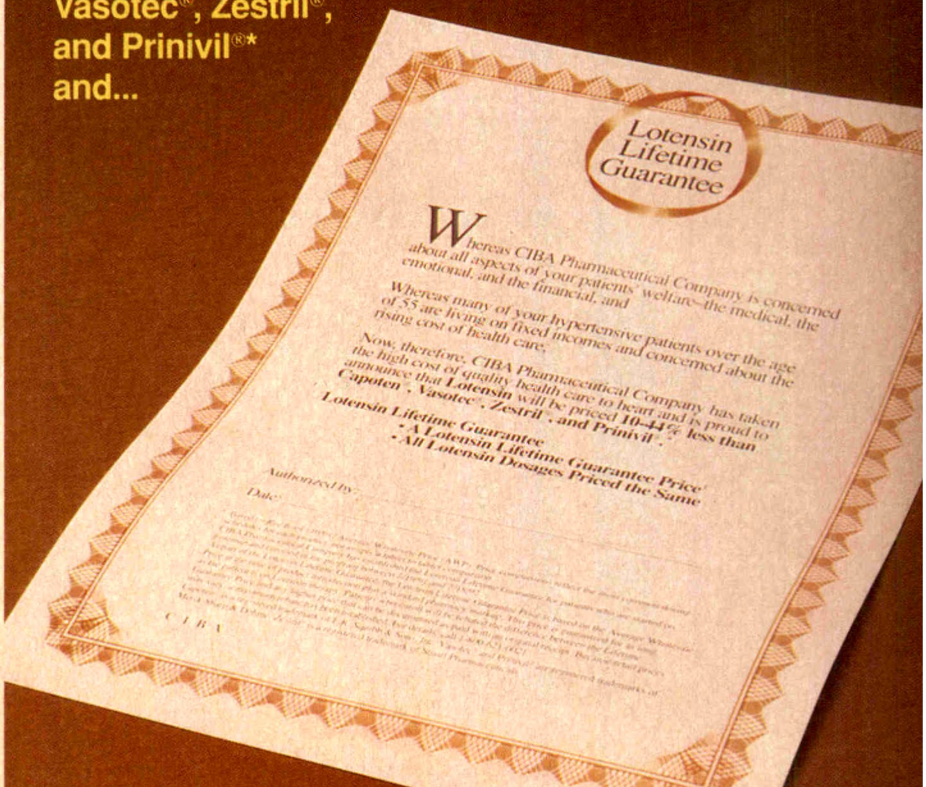

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SYSTEMIC HYPERTENSION

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Circadian Variation in Ventricular Arrhythmias in Hypertensive Men

David Siegel, Dennis M. Black, Dana G. Seeley, and Stephen B. Hulley

The prevalence of ventricular arrhythmias was examined by 24-hour Holter monitoring in hypertensive men without a history of symptomatic cardiac disease. The prevalence of a complex or frequent ventricular arrhythmia was significantly increased ($p < 0.01$) during the interval from 6 A.M. to noon when compared with the interval from midnight to 6 A.M. This suggests that the increased frequency of sudden cardiac death noted in other studies to occur in the morning might be related, at least in part, to an increased frequency of ventricular arrhythmias.

VALVULAR HEART DISEASE

348

Effects of a Single Oral Dose of Captopril on Left Ventricular Performance in Severe Mitral Regurgitation

Thomas Wisenbaugh, Rafique Essop, Christian Rothlisberger, and Pinhas Sareli

Hemodynamic and angiographic measurements were obtained before and 90 minutes after administration of oral captopril (25 to 50 mg) in 18 patients with chronic severe mitral regurgitation, 9 of whom were pretreated with atropine to produce parasympathetic blockade. Captopril reduced left ventricular systolic and diastolic pressures, but angiographic ejection fraction did not improve in either group due in part to a negative inotropic effect that was detected by pressure-volume loop analysis.

355

Comparison of Results of Percutaneous Mitral Valvuloplasty in Patients with Large (>6 cm) Versus Those with Smaller Left Atria

Fernando Alfonso, Carlos Macaya, Andrés Iñiguez, Camino Bañuelos, Rosa Hernandez, Javier Goicolea, Antonio Fernandez-Ortiz, José Zamorano, and Pedro Zarco

To assess the value of percutaneous mitral valvuloplasty in patients with aneurysmatic left atrium (>60 mm on echocardiography) the results of the procedure in 46 consecutive patients with aneurysmatic left atrium (group I) were compared with those of 125 consecutive patients with smaller left atrium (group II). Group I patients were older, more symptomatic, had atrial fibrillation more often and higher echocardiographic scores. Mitral valve area after the procedure was lower in group I patients and dilatation failure without complications was more frequently found in this group. In addition, a suboptimal result (final mitral valve area <1.5 cm^2) was independently related to the presence of an aneurysmatic left atrium. Thus, although percutaneous mitral valvuloplasty may be per-

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formed successfully in patients with mitral stenosis and aneurysmatic left atrium, this cohort of patients more often has technically difficult procedures, dilatation failure and suboptimal results.

361

Hemodynamic Effects of Nitroprusside on Valvular Aortic Stenosis

Hamid Ikram, Clive J.S. Low, Ian G. Crozier, and Teresa Shirlaw

Thirty-five patients with valvular aortic stenosis and a range of left ventricular (LV) ejection fraction were subjected to acute vasodilation with sodium nitroprusside during routine cardiac catheterization. Fourteen patients (group 1) responded with an increase in cardiac index and 21 (group 2) with a decrease. Group 1 was identified by lower LV ejection fraction and cardiac index, smaller aortic valve area and higher LV end-diastolic pressure. These results suggest that balanced vasodilatation may be a therapeutic option in patients with valvular aortic stenosis and impaired LV function who are not suitable for aortic valve replacement.

367

Value of Exercise Doppler Echocardiography in Patients with Prosthetic or Bioprosthetic Cardiac Valves

Renée B.A. van den Brink, Hans A. Verheul, Cees A. Visser, Mark J. W. Koelemay, and Arend J. Dunning

Doppler echocardiographic examination is frequently performed at rest, although this situation is not representative of patients' daily activities. Therefore, a symptom-limited exercise test was performed in 61 asymptomatic patients with mechanical or bioprosthetic valves in the aortic position (n = 29) or mitral position (n = 39) and a normal left ventricular function. In 5 of 61 patients (8%), all with aortic prostheses, no adequate Doppler signals were obtained within 1 minute after the termination of exercise. In patients with aortic prostheses, the responses to exercise could be inferred to a great extent, from the transprosthetic gradient and the maximal flow velocity ratio (i.e., the ratio between the maximal blood flow velocity in the left ventricular outflow tract and the transprosthetic blood flow velocity) at rest. In contrast, the Doppler echocardiographic response to exercise in patients with mitral prostheses proved to be considerably less predictable with Doppler parameters at rest.

CARDIOMYOPATHY

373

Influence of Mitral Regurgitation on the Response to Captopril Therapy for Congestive Heart Failure Caused by Idiopathic Dilated Cardiomyopathy

A. Evangelista-Masip, J. Bruguera-Cortada, R. Serrat-Serradell, A. Robles-Castro, E. Galve-Basilio, M. Alijarde-Guimera, and J. Soler-Soler

To assess the influence of mitral regurgitation (MR) on the response to captopril therapy for congestive heart failure, 30 patients with functional class III CHF were studied. Stroke volume was measured by Doppler echocardiography and exercise tolerance by exercise testing before the start and 1, 3 and 12 months of treatment. Patients were classified into the MR group (n = 14) and non-MR group (n = 16). No significant differences were observed between the groups at pretreatment studies. Exercise tolerance increased significantly in the MR group at 1, 3 and 12 months, but not in the non-MR group. Stroke volume increased significantly only in the MR group at 1 and 3 months; at 12 months, the increase was not significant. The presence of dynamic MR appears to be an important factor in the therapeutic response to captopril therapy for congestive heart failure.

CONGENITAL HEART DISEASE

377

Predictors of Long-Term Survival with Ebstein's Anomaly of the Tricuspid Valve

Thomas L. Gentles, A. Louise Calder, Patricia M. Clarkson, and John M. Neutze

In this retrospective review of 48 patients with Ebstein's anomaly, age at presentation was <1 day to 55 years (median 2.6). The late outcome was similar in patients who presented in the first 3 days of life and survived >6 months and those who presented at >3 months of age. At last review — 4 months to 31 years (median 7.7) after initial presentation — 28 of the 41 patients who survived to age 6 months were alive. Seventeen patients were followed for >10 years. Actuarial survival was 50% at age 47 years. Significant predictors of death were sex (male), cardiothoracic ratio ≥0.65 and New York Heart Association class III or IV, or class II but with cardiothoracic ratio ≥0.65. In the 8 patients who died suddenly, cardiothoracic ratio ≥0.65 was a better predictor of death than functional status. Tricuspid valve surgery resulted in a satisfactory outcome in 7 of 8 patients at an average of 44 months after operation.

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Differences in Circadian Blood Pressure Between Upper and Lower Extremity in Aortic Coarctation Patients With and Without Postoperative Pressure Gradients

Jens Sehested

Coarctation patients with a positive brachial to femoral pressure gradient postoperatively show an increase in this gradient during the nocturnal period of decreasing circulatory activity in contrast to postoperative patients without a positive gradient, suggesting that upper limb vascular abnormalities in coarctation are not fully irreversible and depend on complete relief of the pressure gradient.

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Note: May aid in preventing Calcium Oxaluria

SYMPTOMS: Refractory Hypokalemia, Tremors, and cramping of extremities and tongue, grimaces, myoclonic jerks, Chvostek's sign, ataxia, irritability, disorientation, convulsion, psychotic behavior.

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MISCELLANEOUS

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Systemic Venous Flow During Cardiac Surgery Examined by Intraoperative Transesophageal Echocardiography

Fausto J. Pinto, Bengt Wranne, Frederick G. St. Goar, Lawrence C. Siegel, Gordon Haddow, Ingela Schnittger, and Richard L. Popp

Intraoperative transesophageal echocardiography was used in 21 patients to study changes in systemic venous return during cardiac surgery. Hepatic and pulmonary venous flow, tricuspid annular motion, and signs of tricuspid regurgitation were recorded at 5 different intraoperative times, from before opening of the chest until chest closure after surgery. A significant decrease in systolic flow, an increase in diastolic flow with a decrease in the systolic to diastolic ratio in hepatic venous flow, a decrease in tricuspid annulus motion and no significant tricuspid regurgitation were noted from before to after cardiopulmonary bypass. Right heart dysfunction and mechanical restriction induced by chest closure are suggested as the mechanisms responsible for the changes observed after open heart surgery.

394

Relation of Plain Chest Radiographic Findings to Pulmonary Arterial Pressure and Arterial Blood Oxygen Levels in Patients with Acute Pulmonary Embolism

Paul D. Stein, Christos Athanasoulis, Richard H. Greenspan, and Jerald W. Henry

Abnormalities of the plain chest radiograph of 123 patients with acute pulmonary embolism (PE) and no prior cardiac or pulmonary disease were related to the pulmonary arterial mean pressure, the partial pressure of oxygen in arterial blood, and the alveolar-arterial oxygen gradient. A prominent central pulmonary artery and cardiomegaly indicated a higher pulmonary arterial pressure than did atelectasis, a pulmonary parenchymal abnormality or pleural effusion. The radiographic findings give clues to the severity of pulmonary hypertension in acute PE and suggest that pulmonary infarction or hemorrhage is associated with less severe PE.

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Level and Diurnal Variations of Hormones of Interest to the Cardiovascular System in Patients with Heart Transplants

Jens Sehested, Frank Thomas, Martin Thom, Søren Schifter, Vera Regitz, Søren Sheikh, Wolfgang Oelkers, Ülo Palm, Wolfgang Meyer-Sabellek, and Roland Hetzer

Repeated determinations, over 24 hours, of catecholamines, neuropeptide Y, pancreatic polypeptide, calcitonin gene-related peptide, plasma renin activity, aldosterone, atrial natriuretic factor and cortisol were performed in 10 patients with heart transplants and the results compared with those of 12 age-matched controls. There was no difference between patients and controls for catecholamines and neuropeptide Y. Patients had higher levels of plasma renin activity, calcitonin gene-related peptide and atrial

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natriuretic factor. Abnormal diurnal profiles in patients were found for calcitonin gene-related peptide, aldosterone, atrial natriuretic factor and pancreatic polypeptide. Thus, except for hormones reflecting sympathetic activity, all hormonal systems studied showed abnormalities in blood levels or circadian rhythmicity, or both.

METHODS

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Rate-Corrected Mean Velocity of Fiber Shortening–Stress at Peak Systole as a Load-Independent Measure of Contractility

George G. S. Sandor, Ruby Popov, Eustace De Souza, Starr Morris, and Beverley Johnston

This study examined whether the relation of mean velocity of fiber shortening–stress at peak systole could be used as a simpler method of assessing left ventricular contractility than that of stress at end systole. Twenty-five normal children (mean age 11 years) and six patients with cardiomyopathy (mean age 8 years) were studied. Using echocardiography, blood pressure and carotid pulse tracings, stress at peak and end-systole, and rate-corrected mean velocity of fiber shortening were obtained. The slope of stress at peak systole versus end-systole for both groups was linear and almost approached the line of identity. The relations of fiber shortening–stress at peak systole and end-systole were virtually the same, with a higher intercept for the former. This study confirmed the normal values for these indexes and demonstrated that fiber shortening-stress at peak systole can be used to assess left ventricular contractility.

BRIEF REPORTS

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Comparison of One-, Six- and 24-Hour Ambulatory Electrocardiographic Monitoring for Ventricular Arrhythmia as a Predictor of Mortality in Survivors of Acute Myocardial Infarction

Stuart J. Connolly, and John A. Cairns, on behalf of the CAMIAT Pilot Study Group

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Consequences of a Media Campaign Focusing on Delay in Acute Myocardial Infarction

Marianne Blohm, Johan Herlitz, Marianne Hartford, Björn W. Karlson, Martin Risenfors, Russell V. Luepker, Margareta Sjölin, and Stig Holmberg

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Interobserver Variability in Grading of Coronary Arterial Narrowings Using the American College of Cardiology/American Heart Association Grading Criteria

Neal S. Kleiman, Arsenio R. Rodriguez, and Albert E. Raizner

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*In hypertension, CAPOTEN may be used as initial therapy (25 mg bid or tid) for patients with normal renal function, in whom the risk of neutropenia/agranulocytosis is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

†In heart failure, CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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Lack of Correlation Between the Signal-Averaged Electrocardiogram and Regional Wall Motion Abnormalities in Coronary Artery Disease
Alan Woelfel, David E. Weaver, Mark Jenkins, Linda P. Woelfel, and Margaret C. Herbst

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Usefulness of Transesophageal Echocardiography for Diagnosis of Mitral Valve Prolapse
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Assessment of Relative Sensitivities of Noninvasive Tests for Cardiac Amyloidosis in Documented Cardiac Amyloidosis
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Simultaneous Mechanical Clot Fragmentation and Pharmacologic Thrombolysis in Acute Massive Pulmonary Embolism
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Correction

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Doctors, Save Your Money Because There Will Be Less in the Future

William C. Roberts

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

FEBRUARY 1, 1992, VOL. 69, NO. 4

Enhancement of the Efficacy of Isosorbide Dinitrate by Captopril in Stable Angina Pectoris

Vladimir I. Metelitsa, MD, Sergey Yu. Martsevich, MD,
Marina P. Kozyreva, MD, and Irina D. Slastnikova, MD

This study was designed to assess whether the angiotensin-converting enzyme inhibitor captopril could potentiate the efficacy of a single dose of oral isosorbide dinitrate (ISDN) in patients with coronary artery disease. Fourteen men (mean age 53 years) with stable angina pectoris were studied. In each patient the efficacy of placebo, captopril (50 to 100 mg), ISDN (10 mg), and a combination of captopril (50 to 100 mg) and ISDN (10 mg) was assessed by repeated exercise treadmill tests performed before and 1, 2, 3 and 6 hours after administration of a single dose. A single-blind, randomized technique was applied. According to the mean data in the whole group of 14 patients, captopril alone produced no improvement in exercise duration to the onset of angina and to angina of moderate severity compared with placebo. The magnitude of ST-segment depression did not significantly change after captopril administration. ISDN alone significantly increased exercise duration to onset of angina and to angina of moderate severity (antianginal effect) and decreased the magnitude of ST-segment depression (antiischemic effect) 1 to 3 hours after administration. Combined administration of ISDN and captopril resulted in more expressed antianginal and antiischemic effects; at 2, 3 and 6 hours these effects with ISDN plus captopril were significantly more pronounced than those with ISDN alone.

According to individual data, the most marked potentiation of ISDN efficacy was observed in patients who had poor response to ISDN alone. In all 6 patients in whom ISDN alone was ineffective, after the addition of captopril the desired antianginal effect was obtained. It is concluded that captopril can potentiate the efficacy of nitrates, especially in patients who do not respond to conventional doses.

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The problem of resistance and tolerance to nitrates has been seriously studied in recent years. Several strategies to augment nitrate efficacy have been proposed. Since vascular tolerance to nitrates has been shown to develop when reduced sulfhydryl groups are no longer available,[1,2] using sulfhydryl group donors has been suggested for this purpose. Several experimental[3–7] and clinical[8] studies have shown that vasodilator action of organic nitrates can be more effective with N-acetylcysteine. However, some investigators were unable to demonstrate such beneficial action of N-acetylcysteine.[9–12] Captopril is another compound that contains the sulfhydryl group. The experimental study of Van Gilst et al[13] demonstrated that captopril can increase the vasodilatory effect of isosorbide dinitrate (ISDN).[13] The present study was performed to assess whether captopril could potentiate the antianginal efficacy of a single dose of ISDN in patients with stable angina pectoris.

METHODS

Patients: Fourteen men (mean age 53 years, range 45 to 62) with coronary artery disease and stable angina pectoris were studied. Six patients were in Canadian Cardiovascular Society functional class 2, and 8 were in class 3. Six patients had a history of myocardial infarction ≥6 months before the study. Twelve patients had undergone coronary angiography, which in all cases demonstrated >75% narrowing of the luminal diameter of at least 1 major coronary artery. Angina pectoris was documented by a positive exercise test with both typical symptoms of angina and horizontal or downsloping ST-segment depression of >1 mm in all the patients. Patients with angina at rest, hypertension, congestive heart failure, and liver or renal diseases were not included in the study. No patient received β-adrenoceptor blockers or calcium antagonists before entry into the study.

Study protocol: The study was approved by the Pharmacological Committee of the Ministry of Public Health of the USSR. All patients gave informed consent.

One week before examination all antianginal therapy was discontinued except sublingual nitroglycerin to relieve anginal pain. At the end of the washout period all patients performed a standard graded exercise test

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TABLE I Systolic Blood Pressure at Rest (A) and During Maximal Work Load (B) in 14 Patients

	Time (hours) After Dose				
Drug	0	1	2	3	6
Placebo	A 123 ± 4	120 ± 4	122 ± 3	120 ± 3	124 ± 3
	B 146 ± 4	143 ± 5	143 ± 3	148 ± 4	148 ± 5
Captopril	A 126 ± 3	114 ± 3*	112 ± 3*	110 ± 3†	116 ± 4*
	B 147 ± 3	140 ± 4	138 ± 4	138 ± 3*	140 ± 4
ISDN	A 124 ± 2	110 ± 2*	108 ± 2†	106 ± 3†	121 ± 4
	B 148 ± 4	145 ± 6	139 ± 6 ‡	142 ± 4 ‡	148 ± 3
ISDN plus captopril	A 125 ± 5	104 ± 4†	99 ± 3†	98 ± 3†	105 ± 3†
	B 144 ± 4	142 ± 5	135 ± 4*	132 ± 5*	139 ± 5

Significance of differences with placebo: *p <0.05; ‡p <0.01.
Significance of differences between ISDN and ISDN plus captopril: ‡p <0.05.
ISDN = isosorbide dinitrate.

on a computer-assisted treadmill (ICR Stress Test System), at a speed of 4 km/hour and with the grade increasing every 3 minutes by 4%. Exercise was discontinued when the patient experienced angina of moderate severity (scale 2[14]). After that, individual work loads were adjusted for each patient so that angina pectoris developed between the third and the sixth minutes of exercise. The adjusted work load was repeated 3 to 4 times. Only patients with well-reproduced work loads were admitted into the study.[15]

To analyze the efficacy of the drugs, pharmacodynamic studies on a treadmill were performed. Each pharmacodynamic study included exercise treadmill tests before and repeatedly after single dose administration. Studies with placebo, ISDN (10 mg), captopril (50 to 100 mg) and a combination of ISDN (10 mg) and captopril (50 to 100 mg) were performed in each patient. The interval between 2 consecutive pharmacodynamic studies was ≥2 days. A single-blind, randomized technique was applied. On the day of pharmacodynamic study, 2.5 hours after breakfast, a control exercise test was performed. Then the drug was given (at 10 A.M.) and exercise tests were repeated after 1, 2, 3 and 6 hours. The end point of all exercise tests were strictly the same for every patient and consisted of the development of angina of moderate severity (scale 2). The intensity of angina during exercise was assessed by a 3-point rating scale which the patients were accustomed to using.[14] Electrocardiogram at rest and during exercise was continuously monitored in 12 standard leads on the oscilloscope. The magnitude of ST-segment depression (in V_5 lead) was assessed from the net curves of ST-segment level drawn by a computer-based system. Blood pressure was recorded before exercise in the standing position and every 3 minutes during exercise by the ausculatory method.

Evaluation of the effect: The following parameters were measured from each exercise test: (1) time to the onset of angina (scale 1), (2) time to angina of moderate severity (scale 2), (3) degree of ST-segment depression at identical exercise level (same exercise duration as at the end point of control exercise test), (4) heart rate at rest and during maximal work load, and (5) systolic blood pressure at rest and during maximal work load.

Individual responses to the drugs were assessed in each patient. To accomplish this, the increase in exercise duration to angina of scale 2, compared with the control exercise test, was calculated for every exercise test performed after drug (or placebo) administration. The antinaginal effect was considered sufficient if such an increase in exercise duration after drug administration exceeded the one after placebo administration by ≥2 minutes.

The dose of ISDN was 10 mg in all patients, and the dose of captopril was 100 mg in 11 patients. Three patients with standing systolic blood pressure of <120 mm Hg received captopril 50 mg.

Statistical analysis: The results are presented as mean ± standard error of the mean. The significance of differences was assessed by Student's paired *t* test with the Bonferroni modification. Differences were considered significant for a p value of <0.05.

RESULTS

Placebo: There were no significant changes in systolic blood pressure or heart rate at rest and during exercise after placebo administration (Tables I and II). Placebo did not cause a change in exercise duration to angina pectoris of scale 1 (onset of angina). Exercise duration to angina pectoris of scale 2 (angina of moderate severity) after placebo administration increased slightly and statistically significantly at 2 hours compared with control values (Tables III and IV). Placebo administration did not influence the magnitude of ST-segment depression at an identical work load compared with results after the control exercise test (Table V).

Captopril: At rest, systolic blood pressure significantly decreased (compared with placebo values) 1 hour after captopril administration. This effect was maximal at 3 hours and persisted at 6 hours. Maximal systolic blood pressure during exercise did not change significantly after captopril administration (Table I). Changes in heart rate at rest and during maximal work load after administration of captopril were not statistically significant (Table II).

Captopril produced significant improvement in exercise duration to onset of angina (comparison with placebo) only at 2 hours. Exercise duration to angina of moderate severity increased insignificantly after captopril administration at any time point (Tables III and IV). The magnitude of ST-segment depression at an identical work load after captopril administration did not decrease significantly (Table V).

Isosorbide dinitrate: A significant reduction in systolic blood pressure at rest was observed 1 to 3 hours after ISDN administration. During maximal exercise after administration of ISDN, systolic blood pressure was unchanged (Table I). Heart rate at rest and during maximal exercise increased significantly 1 to 3 hours after ISDN administration (Table II). Exercise duration to onset of angina and angina of moderate severity increased significantly at 1, 2 and 3 hours after ISDN administration compared with corresponding exercise

TABLE II Heart Rate at Rest (A) and During Maximal Work Load (B) in 14 Patients

	Time (hours) After Dose						
Drug	0	1	2		3		6
Placebo	A 78 ± 2	74 ± 3	73 ± 3		71 ± 2		76 ± 3
	B 109 ± 3	109 ± 3	109 ± 3		109 ± 4		110 ± 4
Captopril	A 77 ± 2	77 ± 2	74 ± 2		72 ± 2		74 ± 2
	B 110 ± 3	116 ± 3	111 ± 3		110 ± 3		108 ± 3
ISDN	A 77 ± 2	83 ± 2*	83 ± 3*		81 ± 3*		80 ± 3
	B 110 ± 3	118 ± 3†	118 ± 3†	‡	119 ± 3†	‡	110 ± 3
ISDN plus captopril	A 78 ± 2	83 ± 4	88 ± 4†		89 ± 4†		84 ± 3*
	B 111 ± 3	121 ± 4†	127 ± 3†		125 ± 4†		116 ± 3

Abbreviation and symbols as in Table I.

TABLE III Exercise Duration to Onset of Angina in 14 Patients

	Time (hours) After Dose				
Drug	0	1	2	3	6
Placebo	2.9 ± 0.3	3.2 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	2.6 ± 0.3
Captopril	3.2 ± 0.3	3.6 ± 0.3	4.1 ± 0.4*	3.8 ± 0.3	3.0 ± 0.3
ISDN	2.6 ± 0.3	4.8 ± 0.6*	4.6 ± 0.5*	4.4 ± 0.6*	2.9 ± 0.3
			‡	‡	‡
ISDN plus captopril	2.8 ± 0.3	5.4 ± 0.6*	5.5 ± 0.6†	5.6 ± 0.6†	3.7 ± 0.4*

Abbreviation and symbols as in Table I.

TABLE IV Exercise Duration to Angina of Moderate Severity in 14 Patients

	Time (hours) After Dose				
Drug	0	1	2	3	6
Placebo	3.9 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	4.5 ± 0.4	3.8 ± 0.3
Captopril	4.2 ± 0.3	4.7 ± 0.4	5.2 ± 0.4	4.9 ± 0.4	3.8 ± 0.3
ISDN	3.9 ± 0.3	6.5 ± 0.6*	6.4 ± 0.6*	6.2 ± 0.6*	4.2 ± 0.3
			‡	‡	‡
ISDN plus captopril	4.2 ± 0.3	7.6 ± 0.7†	8.1 ± 0.6†	8.0 ± 0.6†	5.2 ± 0.4*

Abbreviation and symbols as in Table I.

TABLE V Magnitude of ST-Segment Depression (mm) at Identical Work Loads in 14 Patients

	Time (hours) After Dose				
Drug	0	1	2	3	6
Placebo	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.2
Captopril	1.3 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.4 ± 0.1
ISDN	1.4 ± 0.1	1.0 ± 0.1†	0.9 ± 0.1†	0.8 ± 0.1†	1.3 ± 0.1
			‡	‡	‡
ISDN plus captopril	1.4 ± 0.1	0.8 ± 0.1†	0.6 ± 0.1†	0.6 ± 0.1†	1.1 ± 0.1*

Abbreviation and symbols as in Table I.

tests after placebo administration (Tables III and IV). The magnitude of ST-segment depression at an identical work load was significantly less at 1, 2 and 3 hours after ISDN administration than after placebo (Table V).

Isosorbide dinitrate plus captopril: Reduction in systolic blood pressure at rest after combined administration of ISDN and captopril was greater than after either drug given alone; the difference between ISDN and ISDN plus captopril was statistically significant at 2, 3 and 6 hours (Table I). Maximal systolic blood pressure during exercise after combined administration of ISDN and captopril was lower than that after either placebo, captopril or ISDN administration, but this difference was not statistically significant. Heart rate at rest significantly increased 1 to 6 hours after combined administration of ISDN and captopril but this increase was not significantly different from that after administration of ISDN alone (Table II). During exercises after combined administration of ISDN and captopril, patients were able to achieve significantly higher heart rates than during corresponding exercise tests after placebo and after ISDN alone (Table II).

Exercise duration to onset of angina and angina of moderate severity after ISDN plus captopril improved significantly (compared with placebo) at 1, 2, 3 and 6 hours. At 2, 3 and 6 hours the combination of ISDN and captopril increased exercise duration to onset of angina and angina of moderate severity to a significantly greater extent than did either drug alone (Tables III and IV). The magnitude of ST-segment depression at an identical work load decreased significantly at 1, 2, 3 and 6 hours after combined administration of ISDN and captopril (Table V).

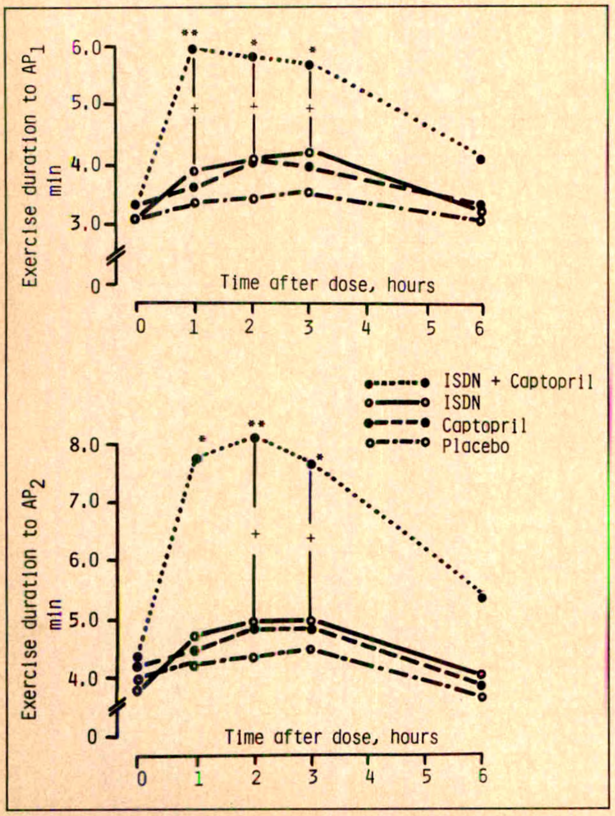

FIGURE 1. Exercise duration to angina of scale 1 (onset of angina, AP_1) and scale 2 (angina of moderate severity, AP_2) in 6 patients with poor response to isosorbide dinitrate (ISDN) alone. Significance of differences versus placebo: * $p < 0.05$; ** $p < 0.01$. Significance of differences between ISDN alone and ISDN plus captopril: $^+$ $p < 0.05$.

Individual analysis: Large interindividual differences between the efficacy of ISDN alone and ISDN plus captopril were observed. In 10 patients, combined administration of ISDN and captopril was more effective than administration of ISDN alone (the difference in exercise duration to angina of moderate severity between ISDN and ISDN plus captopril 2 after administration was >1 minute). In 1 patient ISDN plus captopril were less effective than ISDN alone. In 3 patients ISDN alone and ISDN plus captopril were equally effective. In 6 patients the antianginal efficacy of ISDN was insufficient (according to the accepted criteria). Captopril alone was also ineffective in these 6 patients. The desired antianginal effect was obtained in all patients after combined administration of ISDN and captopril.

Figures 1 and 2 show mean data of the 6 abovementioned patients with poor response to ISDN alone. The baseline exercise parameters (time to onset of angina and angina of moderate severity, magnitude of ST-segment depression) in this subgroup of patients did not differ from the values recorded in the whole group of 14 patients. ISDN alone produced no significant improvement in exercise duration to onset of angina and angina of moderate severity and in ST-segment depression in these 6 patients. By contrast, combined administration of ISDN and captopril resulted in a dramatic increase (nearly 2 times compared with placebo) in exercise duration in this subgroup of patients. Reduction in the magnitude of ST-segment depression mirrored an increase in treadmill walking time after administration of ISDN plus captopril in this subgroup of ISDN poor responders.

Figure 3 is of a patient who had poor response to ISDN alone and the obvious effect of ISDN plus captopril.

Adverse reactions: Captopril alone produced no adverse effects. Headaches were reported by 2 patients after ISDN alone and by 5 patients after ISDN plus captopril. Two patients experienced dizziness 2 hours after ISDN plus captopril, which substantially diminished at 3 hours and completely disappeared at 6 hours.

DISCUSSION

The results of the present study support the previous experimental investigation in which captopril has been shown to increase the effects of ISDN.[13] Our study demonstrates that captopril substantially improves the efficacy of acutely administrated ISDN in patients with stable angina pectoris. According to the mean data in the whole group of patients, combined administration of ISDN and captopril resulted in more pronounced circulatory, antianginal and antiischemic effects than those of ISDN alone. A significant difference between the efficacy of ISDN alone and ISDN plus captopril was seen from the second to the sixth hour after administration.

Six hours after administration when ISDN alone was completely ineffective, the combined administration of ISDN and captopril exerted significant antianginal and antiischemic effects. If we exclude the possible influence of captopril on the pharmacokinetics of ISDN, then we must assume that captopril increases sensitivity to the pharmacologic action of the nitrate.

The observed increase in the efficacy after combined administration of ISDN and captopril was probably not a mere sum of the effects of 2 drugs since captopril alone had a relatively weak antianginal effect that was significant only 2 hours after dosing.

Individual analysis of our data showed some remarkable findings. The difference between efficacy of ISDN alone and ISDN plus captopril varied substantially in different patients. In 4 of them, combined administration of ISDN and captopril was not more effective than administration of ISDN alone. In 10 patients the efficacy of a combination of ISDN and captopril was substantially greater than that of ISDN alone. The most pronounced improvement in the efficacy of ISDN after the addition of captopril was noted in 6 patients who had poor response to ISDN alone.

Several drugs that can be a source of reduced sulfhydryl groups (N-acetylcysteine, methionine) have been shown to potentiate the hemodynamic effects of nitrates as well as partially reverse nitrate tolerance after chronic administration.[3-5] Levy et al[16] showed that patients "initially with the greatest nitroglycerin requirements to reach hemodynamic endpoints exhibited the most dra-

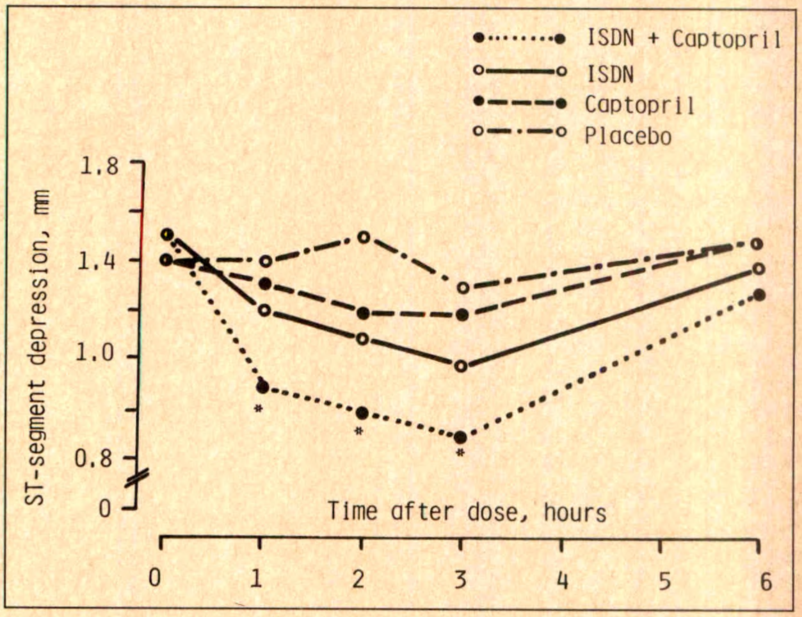

FIGURE 2. Magnitude of ST-segment depression at identical work loads in 6 patients with poor response to isosorbide dinitrate (ISDN) alone. For significance of differences see Figure 1.

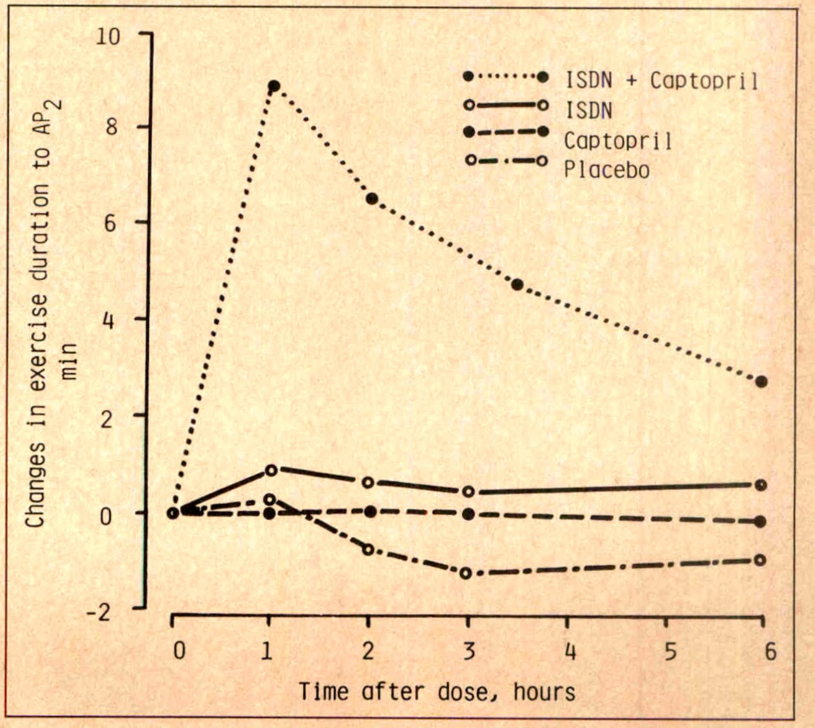

FIGURE 3. Case presentation. Patient with poor response to isosorbide dinitrate (ISDN) alone. Changes in exercise duration to angina of moderate severity (AP_2) from control work load are shown.

matic response to methionine."[16] They proposed that a relative sulfhydryl deficiency in these patients would be a possible explanation for this observed nitroglycerin resistance and methionine sensitivity. This hypothesis can be said to conform to the data of the present work. It can be assumed that patients with poor efficacy of ISDN alone belonged to this subgroup of patients. The addition of captopril, a source of sulfhydryl groups, resulted in the most dramatic augmentation of the effect especially in these patients.

It is necessary to point out that the ability of sulfhydryl group donors to potentiate nitrate effectiveness is recognized by few investigators. In a series of experimental and clinical studies no influence of N-acetylcysteine over nitrate efficacy was revealed.[9-12] Therefore, the ability of captopril to potentiate the efficacy of ISDN seen in this study is a consequence of some other effect of this angiotensin-converting enzyme inhibitor. Recently, enhanced activation of the renin-angiotensin system and increased plasma norepinephrine levels were seen to correlate with resistance to transdermal nitroglycerin in angina pectoris.[17,18] It was also shown that increased intravascular volume and neurohumoral activation may contribute to the genesis of nitroglycerin tolerance in congestive heart failure.[19] To establish the exact mechanism of nitrate efficacy potentiation by captopril, it seems necessary to compare the influence of captopril over nitrate efficacy with that of some other nonsulfhydryl-containing angiotensin-converting enzyme inhibitor and with that of sulfhydryl group donors without angiotensin-converting enzyme inhibitor activity.

Clinical implications: The ability of captopril to potentiate nitrate efficacy can prove useful in a clinical setting. Horowitz et al[20] showed that combined administration of nitroglycerin and N-acetylcysteine may augment the clinical efficacy of nitroglycerin in patients with unstable angina.[20] It cannot be excluded that captopril would have similar properties. It is possible that co-administration of ISDN and captopril will allow patients to overcome initial resistance to nitrates.[21] It is also possible that addition of captopril may be able to reverse or prevent tolerance during sustained nitrate exposure.

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Identifying Coronary Artery Disease in Women by Heart Rate Adjustment of ST-Segment Depression and Improved Performance of Linear Regression Over Simple Averaging Method with Comparison to Standard Criteria

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Performance of exercise electrocardiography for the detection of coronary artery disease (CAD) in women has been limited by relatively poor sensitivity and specificity of standard test criteria. Recent studies suggest that diagnostic methods incorporating heart rate (HR) adjustment of ST-segment depression during exercise may improve the accuracy of exercise testing in women, but the relative performance of different rate-adjusted methods for this purpose is unknown. To assess the effect of gender on relative test performance of the ST-segment/HR (ST/HR) slope, the simple ST/HR index, the HR-recovery loop, and standard ST-depression criteria for the identification of CAD, the exercise electrocardiograms of 254 patients with known or suspected CAD (67 women and 187 men) and of 150 clinically normal subjects (29 women and 121 men) were analyzed. Specificity of each method was comparable in men and women: ST/HR slope 98% (118 of 121) vs 97% (28 of 29), ST/HR index 97% (117 of 121) vs 97% (28 of 29), and HR-recovery loop 96% (116 of 121) vs 93% (27 of 29). In contrast, although there was no difference in sensitivity of the ST/HR slope (95% [177 of 187] vs 93% [62 of 67]; p = not significant [NS]) or HR-recovery loop (90% [168 of 187] vs 87% [58 of 67]; p = NS) between men and women, the ST/HR index was less sensitive for CAD in women than in men (82% [55 of 67] vs 93% [173 of 187]; p <0.05). Thus, among women sensitivity of the simple ST/HR index was lower than that of the ST/HR slope for CAD (82 vs 93%; p <0.05), but there was no significant difference in performance of these 2 methods in men (93 vs 95%; p = NS). Each of the HR-adjusted methods was significantly more sensitive than were standard test criteria at comparable specificity in men and women. These findings support use of the more complex ST/HR slope method for the detection of CAD in women.

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Standard exercise electrocardiographic criteria based on magnitude, time course, and configuration of ST-segment depression have poorer overall test performance for the detection of coronary artery disease (CAD) in women than in men.[1-5] The lower predictive values of standard test findings in women have been explained by the combined effects of low prevalence of CAD[1,2] and low specificity of these criteria in women.[3-5] These findings have limited the clinical use of exercise testing in women.

Heart rate (HR) adjustment of ST-segment depression using the simple ST-segment/HR (ST/HR) index, the computationally more complex ST/HR slope and the HR-recovery loop was reported to improve the accuracy of the exercise electrocardiogram for the identification of CAD.[6-19] Recent studies demonstrated that HR adjustment of the magnitude of ST-segment depression using the simple ST/HR index can improve the exercise electrocardiographic detection of CAD in women,[6,7] but calculation of the linear regression-based ST/HR slope, and construction of the HR-recovery loop were not performed in these reports,[6,7] and sensitivity of the ST/HR index in these women was lower than that reported in other predominantly male populations.[8,9] Therefore, to examine the potential effects of gender on test outcome of these methods we compared the relative performance of the ST/HR slope and index, the HR-recovery loop and standard criteria for the identification of CAD separately in men and in women.

METHODS

Study population: There were 404 consecutively studied subjects and patients who met criteria outlined later and who were entered into 1 of 3 clinical groups: 1 with a low likelihood of CAD, and 2 with a high (or certain) likelihood. All subjects and patients were assigned to 1 of the clinical groups before examination of the exercise electrocardiogram, and no study was excluded after group assignment.

Normal subjects: There were 150 normal subjects (group 1: 121 men and 29 women, mean age 47 ± 12 years). Each subject was referred by a physician for exercise electrocardiography as part of a comprehensive screening evaluation or as a precautionary evaluation before beginning an exercise program. All subjects were free of chest pain, had no history of cardiac disease, were not taking medications, had normal cardiac physical examinations, blood pressure and rest electrocardiograms, and were free of chest pain during treadmill exercise. Based on the data of Diamond et al,[20,21] the age- and sex-adjusted likelihood of CAD in this asymptomatic group can be estimated as ≤ 0.05.

Patients with clinical angina: There were 100 patients with clinical angina (group 2: 59 men and 41 women, mean age 62 ± 10 years). Each patient was referred by a physician for exercise electrocardiography to evaluate clinically stable retrosternal chest discomfort that was consistently provoked by exertion and relieved by rest, and all developed typical chest discomfort during treadmill exercise. Patients with left bundle branch block or myocardial infarction within 8 weeks were not included. There were 10 patients with resting electrocardiographic evidence of previous Q-wave myocardial infarction, and 5 with evidence of left ventricular hypertrophy. There were 63 patients who were not receiving medications; of the remaining 37, 23 were receiving β-blocking drugs, 16 nitrates and 12 calcium antagonists at the time of exercise testing. The age- and sex-adjusted likelihood of CAD in this group can be estimated at >0.93.[20,21]

Patients with catheterization-proved coronary artery disease: There were 154 patients with CAD proved by catheterization (group 3: 128 men and 26 women, mean age 59 ± 9 years). All patients in this group had stable, effort-related chest pain that was relieved by rest, and each was referred by a physician for exercise testing and coronary arteriography. Patients with left bundle branch block or recent myocardial infarction were excluded. There were 24 patients with electrocardiographic evidence of previous Q-wave myocardial infarction, and 13 with evidence of left ventricular hypertrophy. There were 23 patients who were unmedicated; of the remaining 131 patients, 104 were receiving β-blocking drugs, 85 nitrates and 82 calcium antagonists.

Exercise electrocardiography: Exercise electrocardiography was performed on a treadmill using a computerized exercise system (Q5000 exercise system, Quinton Instrument Co., Seattle, Washington, or a CASE 2 or 12 exercise system, Marquette Electronics, Milwaukee, Wisconsin) modified by the addition of a bipolar lead CM5. All patients exercised according to the Cornell protocol,[22,23] and age-adjusted target HRs were sought as the exercise end point for all studies. In addition, computer-calculated ST-segment amplitudes, measured to the nearest 10 μV at a point 60 ms after the J point with the end of the PR segment as a reference, were obtained in each lead after each stage of exercise, at peak exercise and after each minute of recovery; accuracy of this measurement was previously validated in our laboratory.[22,23]

Exercise tests were evaluated using standard electrocardiographic criteria based on the measured amount of ST-segment depression on the peak exercise electrocardiogram.[9,18] The test was considered positive in the presence of 0.1 mV (100 μV) of additional horizontal or downsloping ST-segment depression. The test was considered negative in the presence of any amount of upsloping ST-segment depression or if <0.1 mV of additional horizontal or downsloping ST-segment depression was present at end-exercise.[9,18]

ST-segment/heart rate slope and index calculation: Calculation of the maximal ST/HR slope was performed by linear regression analysis to relate the measured amount of ST-segment depression in each lead (except aVR, aVL and V_1) to the HR at the end of each stage of exercise and at peak exercise, according to methods previously reported in detail.[9,12,18,22,23] All ST-segment measurements were obtained at 60 ms after the J point. After calculation of the maximal ST/HR slope in each lead, the highest ST/HR slope with a significant coefficient of correlation among all the leads was taken as the test result, reported as μV/beat/min. The ST/HR index (also reported as μV/beat/min) was calculated by dividing the maximal additional ST-segment depression at end-exercise (corrected for any resting ST-segment depression in that lead on the upright preexercise control electrocardiogram) by the exercise-induced change in HR.[15,16,18]

Rate–recovery loop construction: The recovery phase pattern of ST-segment depression with reference to changing HR (the HR-recovery loop) was examined by constructing continuous plots of absolute ST-segment deviation and HR throughout treadmill exercise and recovery.[19] For each subject and patient, ST-segment depression was plotted in the upward direction on the vertical axis as a function of HR during exercise and recovery on the horizontal axis; the resulting loop pattern was determined by the relation of early recovery phase ST depression to end-exercise ST depression at corresponding HR.

In clinically normal subjects, because less ST-segment depression is present at early recovery phase HR than at corresponding exercise HR, there is a clockwise loop of ST-segment depression as a function of HR during exercise and recovery. This pattern was defined as a normal HR-recovery loop.[19] In patients with CAD, because ST-segment depression is usually greater at early recovery phase HR than at corresponding exercise phase HR, there is a counterclockwise loop of ST-segment depression as a function of HR during exercise and recovery. This pattern was defined as an abnormal HR-recovery loop.[19]

Coronary angiography: In group 3, selective coronary cineangiography was performed with the Judkins technique, with multiple views obtained in all patients. The films were interpreted separately from the original clinical report, specifically for study purposes, as previously reported in detail.[15,18]

Degree of stenosis was defined as the greatest percent reduction of luminal diameter in any view as compared with the nearest normal segment. For classification of the number of obstructed coronary arteries, CAD was considered significant when 50% luminal diameter obstruction was present. Left main narrowing $\geq 50\%$ was scored as the equivalent of 2-vessel CAD.[15,18] According to these criteria there were 37 patients with 1-vessel CAD, 50 with 2-vessel, and 67 with

TABLE I Group Characteristics and Exercise Performance

	Clinically Normal			Clinical Angina			CAD by Catheterization		
Characteristics	Men (n = 121)	p Value	Women (n = 29)	Men (n = 59)	p Value	Women (n = 41)	Men (n = 128)	p Value	Women (n = 26)
Age (yr)	47 ± 11	NS	50 ± 14	61 ± 9	NS	63 ± 12	58 ± 9	NS	61 ± 8
Exercise duration (min)	18.3 ± 2.5	<0.001	15.4 ± 4.5	11.4 ± 4.3	<0.05	9.9 ± 2.9	9.9 ± 3.8	<0.001	7.3 ± 2.6
Proportion of target heart rate achieved (%)	94 ± 6	NS	90 ± 10	74 ± 14	<0.05	70 ± 12	67 ± 10	NS	64 ± 11
Peak heart rate (beats/minute)	166 ± 12	<0.05	158 ± 21	125 ± 23	<0.05	133 ± 22	114 ± 17	NS	108 ± 21
Peak systolic blood pressure (mm Hg)	182 ± 18	<0.001	167 ± 22	166 ± 26	<0.05	175 ± 27	156 ± 22	<0.05	166 ± 21
ST depression (μV)	41 ± 51	NS	50 ± 45	188 ± 85	<0.05	144 ± 58	217 ± 124	<0.01	155 ± 76
Electrocardiographic Q-wave infarction (%)	0	NS	0	14	NS	5	16	NS	15
β-blockers (%)	0	NS	0	24	NS	22	66	NS	77
Calcium antagonists (%)	0	NS	0	14	NS	10	50	NS	65
Nitrates (%)	0	NS	0	17	NS	15	52	NS	69

CAD = coronary artery disease; NS = not significant.

TABLE II Test Sensitivity and Specificity of Standard and Heart Rate-Adjusted ST-Depression Criteria for the Identification of Coronary Artery Disease in Men and Women

Criteria	Men	p Value	Women
ST/HR slope			
>2.40 μV/beat/min			
Specificity	98% (118 of 121)	NS	97% (28 of 29)
Sensitivity	95% (177 of 187)	NS	93% (62 of 67)
ST/HR index			
>1.60 μV/beat/min			
Specificity	97% (117 of 121)	NS	97% (28 of 29)
Sensitivity	93% (173 of 187)	<0.05	82% (55 of 67)*
HR-recovery loop			
Specificity	96% (116 of 121)	NS	93% (27 of 29)
Sensitivity	90% (168 of 187)	NS	87% (58 of 67)
Standard criteria			
Specificity	99% (120 of 121)	NS	93% (27 of 29)
Sensitivity	67% (125 of 187)†	NS	60% (40 of 67)‡
ST depression			
>150 μV			
Specificity	96% (116 of 121)	NS	100% (29 of 29)
Sensitivity	61% (114 of 187)†	<0.01	42% (28 of 67)‡

*p <0.05 vs ST/HR slope sensitivity in women; †p <0.001 vs ST/HR slope and index, and rate-recovery loop sensitivity in men; ‡p <0.001 vs ST/HR slope and index, and rate-recovery loop sensitivity in women.

HR = heart rate; NS = not significant.

3-vessel. There were 14 patients with left main CAD, including 2 with additional 1-vessel CAD, 5 with additional 2-vessel, and 6 with additional 3-vessel.

Data analysis and statistical methods: Definitions of test sensitivity and specificity conform to standard use. Test specificity for each method was defined in the 150 clinically normal subjects (group 1). Because of the highly referred nature of our angiography population, and the known and potential effects of referral bias on selection for angiography,[24,25] test sensitivity was assessed in all 254 patients with known or suspected CAD (groups 2 and 3). Sensitivity and specificity of standard criteria, ST-segment depression at peak exercise, ST/HR index and slope, and HR-recovery loop in men and women were compared using a 2-tailed Fisher's exact test. Comparison of test sensitivity between different criteria among men and women was performed using McNemar's modification of the chi-square method for paired proportions. Because sensitivity and specificity of a test are dependent on the partition value chosen for test positivity, test accuracy of ST-segment depression, and ST/HR index and slope were also compared using receiver-operating characteristic curve analysis. Receiver-operating characteristic curves were compared statistically by means of a univariate Z score test of the difference between the areas under 2 curves.[26]

Mean values for all findings are reported with the standard deviation as the index of dispersion. Comparison of mean values between and among groups was performed by 1-way analysis of variance, with posthoc testing of individual group differences by Scheffe's method. Comparison of subgroup proportions was performed by chi-square analysis with correction for continuity, or a 2-tailed Fisher's exact test. For all comparisons, a p value <0.05 was needed for rejection of the null hypothesis.

RESULTS

Group characteristics and exercise performance: Group characteristics and exercise performance according to sex are shown in Table I. Of the normal subjects (group 1), men and women were similar with respect to mean age, percentage of maximal predicted HR achieved, and magnitude of ST-segment depression at peak exercise. However, the clinically normal women exercised for a shorter period of time and to significantly lower peak HR and systolic blood pressures than did the normal male subjects. Of patients with typical angina (group 2) or known CAD (group 3), men and women were similar with respect to mean age, and women exercised for a shorter period of time, but to higher peak systolic blood pressures, and developed significantly less ST-segment depression than did the men in each group. In addition, although the men and women in group 3 were similar with respect to both percentage of and absolute peak HR achieved, the women in group 2 on average achieved a lower percentage of predicted HR and lower peak HR than did the men.

Of additional factors that may be expected to influence the ST-segment response to exercise, the men and women in both groups 2 and 3 were similar with respect to the proportion of patients receiving β-blockers, calcium antagonists or long-acting nitrates (Table I). There was no difference in the prevalence of electrocardiographic Q-wave myocardial infarction between men and women in each group. Further, there was no difference in the prevalence of 3-vessel (45% [58 of 128] vs 35% [9 of 26]; p = not significant [NS]) or multivessel (76% [98 of 126] vs 73% [19 of 26]; p = NS) CAD between men and women who underwent coronary arteriography.

Relation of test performance to gender: The relative test performances of standard and HR-adjusted ST-segment depression criteria in men and women are compared in Table II and Figure 1. Specificity of the ST/HR slope (2.40 μV/beat/min) and index (1.60 μV/beat/min) partitions were comparable in men and women: 98 vs 97% for the ST/HR slope, and 97 vs 97% for the ST/HR index. There was no difference in sensitivity of the ST/HR slope in men or women (95 vs 93%; p = NS). In contrast, the simple ST/HR index partition of 1.60 was significantly less sensitive for the detection of coronary disease in women than in men (82 vs 93%; $p < 0.05$). Comparison of receiver-operating characteristic curves confirmed the similar overall test performance of the ST/HR slope in men and women, and demonstrated that the lower overall test performance of the ST/HR index in women compared with that in men was independent of test partition selection (Figure 1). There was no significant difference in test performance of the HR–recovery loop between men and women (Table II). For non–HR-adjusted ST-segment criteria, an ST-segment depression partition of 150 μV with 96% specificity in men and 100% specificity in women had significantly lower sensitivity for the detection of CAD in women than in men (42 vs 61%; $p < 0.01$), and standard test criteria demonstrated trends toward lower test specificity and sensitivity in women than in men (Table II).

As a consequence, sensitivity of the ST/HR slope was significantly greater than sensitivity of the ST/HR index in women with CAD (93 vs 82%; $p < 0.05$). In contrast, there was no difference in sensitivity of the ST/HR slope and index in men (95 vs 93%; p = NS). Comparison of receiver-operating characteristic curves confirmed the superior overall performance of the ST/HR slope in women, and further confirmed the sim-

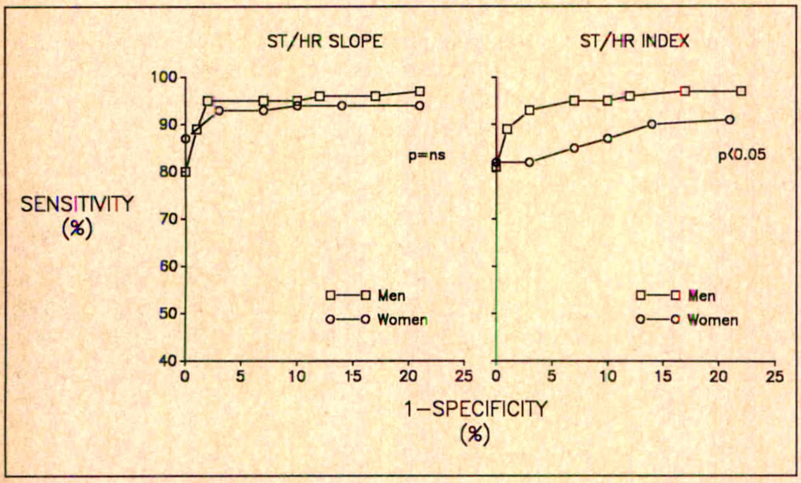

FIGURE 1. Receiver-operating characteristic curves comparing overall performance of ST-segment/heart rate (ST/HR) slope and index for identification of coronary artery disease in men compared with in women. ns = not significant.

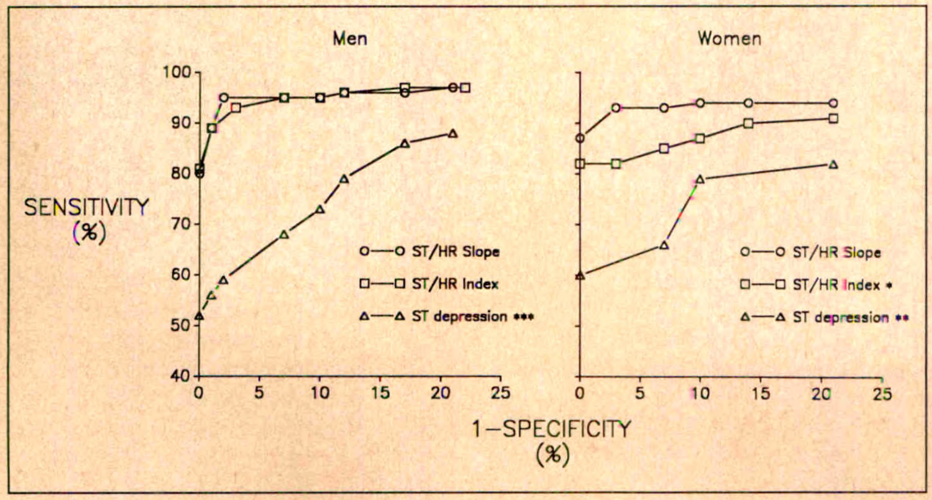

FIGURE 2. Receiver-operating characteristic curves comparing overall performance of ST-segment/heart rate (ST/HR) slope and index, and ST-segment depression for identification of coronary artery disease in men *(left)* and women *(right)*. *p <0.05 vs ST/HR slope; **p <0.01 vs ST/HR slope and index; ***p <0.001 vs ST/HR slope and index.

ilar overall performance of the ST/HR slope and index in men (Figure 2). In both men and women, sensitivity and overall performance of the ST/HR slope and index, and HR-recovery loop were each significantly greater than performance characteristics of ST-segment depression magnitude alone and standard test criteria (Table II and Figure 2).

DISCUSSION

These data demonstrate a differential performance of the ST/HR slope and ST/HR index methods for the identification of CAD in men and in women. Despite improved accuracy of each of the HR adjusted indices as compared with more traditional ST segment criteria independent of patient gender, these findings support the use of the more complex ST/HR slope method for the optimal detection of CAD in women.

Heart rate adjustment of ST depression in women: HR adjustment of ST-segment depression using the simple ST/HR index was previously shown to improve both the exercise electrocardiographic identification of CAD[6,7] and prediction of future coronary events[27] in women. Deckers et al[6] demonstrated that an ST/HR index criterion with 90% specificity had a sensitivity of 77% for angiographically proven CAD, which was substantially better than the 41% sensitivity of the simple change in ST depression with exercise, higher than the 60 and 70% sensitivity of the linear discriminant analyses of Barolsky et al[4] and Detry et al,[2] and similar to the 73% sensitivity of a best fit linear discriminant function derived from the test population.[6] Robert et al[7] also demonstrated in women that simple HR adjustment of ST depression using the ST/HR index improved overall performance for the detection of CAD compared with that of conventional ST depression, but that overall accuracy was further improved by using a logistic discriminant function that incorporated peak exercise ST depression, HR and work load. We previously demonstrated that the ST/HR index and HR–recovery loop can improve risk stratification in asymptomatic women from the Framingham Offspring Study cohort.[27]

Compared with the simple ST/HR index, the regression-based ST/HR slope method further improves accuracy of the exercise electrocardiogram for the detection of CAD in women; there was comparable performance of the ST/HR slope in women and men. Differential performance of the ST/HR index in men and women can not be attributed to any differences in severity of CAD, previous infarction or use of cardioactive medications (Table I). However, the shorter duration of exercise combined with the lower magnitude of ST depression in women with CAD suggest a possible reason for the poorer performance of the ST/HR index than the ST/HR slope in this group. Whereas the ST/HR slope is dependent on the peak-exercise change in ST-segment depression as a function of HR, the ST/HR index examines the average rather than maximal change of ST-segment depression that occurs with HR over the entire course of exercise. As a result, the simple ST/HR index can be more affected by differences in exercise duration and magnitude of ST-segment depression than can the ST/HR slope.[12,28] Because direction of the HR–recovery loop is not dependent on attainment of any threshold magnitude of ST-segment depression at peak exercise,[19] similar test performance of the HR–recovery loop in men and women occurs independent of differences in magnitude of ST-segment depression in these groups.

Exercise electrocardiographic detection of coronary artery disease in women: The basis for the lower overall performance of traditional ST-segment depression criteria for the identification of CAD in women remains controversial.[1–7,29,30] Several studies found no significant differences in either test sensitivity or specificity of standard ST-segment depression criteria in women and men, and attributed the substantially lower positive predictive values for CAD in women to the markedly lower prevalence of CAD in their female study populations.[1,2] However, when a large subgroup of men and women from the Coronary Artery Surgery Study[3] was matched for age, prevalence and severity of CAD, there was no significant difference in test sensitivity between women and men (76 vs 78%; $p = NS$), but specificity was significantly lower in women (64 vs 73%; $p < 0.02$), leading to a lower overall test performance. The study of Deckers et al[5] demonstrating greater amounts of ST depression at any given HR in 116 healthy female volunteers than in a similar group of healthy male volunteers further suggested a lower specificity of standard criteria in women than in men. Differences in the magnitude of ST depression in otherwise healthy women than in men may be due to the effects of either endogenous estrogens or progesterones on the ST-segment response to exercise in women[29,30]; further study of these observations is needed. The trends toward lower specificity and sensitivity of standard test criteria, and the lower sensitivity of the magnitude of ST-segment depression at similar specificity found in the present study, are consistent with these previous observations.

Clinical implications: Exercise electrocardiography in women presents specific diagnostic problems. The low sensitivity of standard test criteria in women results in underdiagnosis of CAD,[1–4,6,7] and because the prevalence of CAD is lower in women, the positive predictive accuracy of exercise testing will be lower in women than in men unless methods with higher sensitivity and specificity are developed. The results of the present study indicate that this is accomplished by the linear regression-based ST/HR slope, but test sensitivity is not improved to the same extent in women by the simple ST/HR index. The concomitant high specificity of the ST/HR slope should minimize the proportion of false positive test results in women, but it must be recognized that ultimate limitation of positive predictive value in low-risk populations is a Bayesian consequence of any imperfect test.[20,21]

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Usefulness of Exercise-Induced ST-Segment Depression in the Inferior Leads During Exercise Testing as a Marker for Coronary Artery Disease

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Multiple lead systems are shown to have a higher sensitivity than that of single leads for detecting coronary artery disease (CAD) during exercise testing, but the value of ST-segment depression isolated to the inferior leads is questionable. To ascertain the diagnostic accuracy of inferior limb lead II compared with that of precordial lead V_5, a retrospective analysis of 173 men was performed (108 in a training population and 65 in a validation cohort). All patients had a standard exercise test and underwent diagnostic coronary angiography within 15 days of the exercise test (range 1 to 65). Sixty-three patients had ≥1 coronary stenoses ≥70%, or left main lesion ≥50%, whereas 45 patients in the training population did not. Exclusion criteria were female sex, left ventricular hypertrophy, left bundle branch block or resting ST-segment depression on the baseline electrocardiogram, previous myocardial infarction or revascularization procedures, and any significant valvular or congenital heart disease. Lead V_5 had a better combination of sensitivity (65%) and specificity (84%) (chi-square = 24.11; p <0.001) than that of lead II (sensitivity 71%, specificity 44%) (chi-square = 2.25; p = 0.13) at a single cut point, and this improved specificity was substantial (95% confidence interval for observed difference 22 to 58%). Receiver-operating characteristic curve analysis also revealed that lead V_5 (area = 0.759) was markedly superior to lead II (area = 0.582) over multiple cut points (z = 3.032; 2p = 0.002). In fact, the area under the lead II curve (0.582) was not significantly >0.50 (z = 1.465; p = 0.07), suggesting that for the identification of CAD, isolated ST-segment depression in lead II is unreliable. In patients with normal electrocardiograms, precordial lead V_5 is a better marker for CAD during exercise testing than is limb lead II. Exercise-induced ST-segment depression isolated to the inferior leads is of little value.

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The standard exercise test continues to be a valuable tool for the evaluation of coronary artery disease (CAD).[1] Use of multiple lead systems is shown to be more sensitive than than that of single leads as markers for CAD,[2,3] but electrocardiographic changes in the inferior leads are of questionable use.[3] This study directly compares ST-segment depression in limb lead II with that in precordial lead V_5 as markers for CAD during exercise testing.

METHODS

Patient selection: TRAINING SET: Subjects were selected consecutively from a group of 2,235 patients who underwent routine clinical exercise testing at the Long Beach Veterans Affairs Medical Center for signs or symptoms suggestive of CAD between August 1984 and January 1990. Of these patients, approximately 32% also underwent coronary angiography within 3 months of testing. After excluding women, patients with left bundle branch block, left ventricular hypertrophy or resting ST-segment depression on their baseline electrocardiograms, those with prior coronary artery bypass surgery or percutaneous transluminal coronary angioplasty, or history or electrocardiographic evidence of myocardial infarction, those receiving digitalis, and those with significant valvular or congenital heart disease, 108 patients remained. Q-waves were considered diagnostic if they occurred in 2 adjacent leads, and were 40 ms in duration and 25% in amplitude of the following R-wave. The electrocardiographic diagnosis of left ventricular hypertrophy was performed using the criteria of Romhilt and Estes.[4] The data was entered into a computerized database (R:Base, Microrim, Redman, Washington) in a prospective fashion, with the analysis performed retrospectively. Two groups were formed: the "No CAD" group consisted of 45 patients without any coronary stenoses ≥70% or left main stenoses ≥50%, or both, identified by coronary arteriography; and the "CAD" group had 63 patients with ≥1 stenoses.

TEST SET: Sixty-five consecutive men referred for evaluation at the Hungarian Institute of Cardiology for CAD who met the previous criteria in 1988 were studied.

Exercise testing: A standard exercise test was performed using a Mortara EliXR treadmill system (Mortara Instruments, Milwaukee, Wisconsin), according to the United States Air Force School of Aerospace Medicine protocol.[5] Briefly, after a maximal treadmill speed is quickly attained (one appropriate to the patient's ability), this speed is kept constant, and only the grade of the treadmill is increased to increase the work load. Blood pressure was measured noninvasively using manual sphygmomanometry at rest in the supine and standing positions every 2 minutes during exercise, immediately after exercise and at 2 and 5 minutes into recovery while in the supine position. A baseline standing 12-lead electrocardiogram was obtained immediately before exercise. Leads II, V_1 and V_5 were monitored continuously during exercise, and a 12-lead electrocardiogram was obtained every 2 minutes during exercise and recovery. All tests were sign/symptom-limited maximal tests using standard criteria for stopping, including serious dysrhythmias, decrease in systolic blood pressure below level at rest, >4 mm ST-segment depression or elevation, severe angina pectoris and central nervous system complaints. When the end point was reached, the treadmill was stopped abruptly, and the patient placed in the supine position within 1 minute.

At the Hungarian Institute of Cardiology, the test set performed supine bicycle exercise testing. Because both control subjects and patients with CAD were subjected to the same criteria for an abnormal response it was thought unimportant that this test gives different physiologic responses than those of upright treadmill testing, since it was not meant to be a comparison of exercise protocols. Work load on the bicycle was achieved by increasing the tension against which the pedals were pushed.

Computer analysis of the exercise electrocardiogram: Microprocessor-based exercise electrocardiographic devices have been used since May 1987 at both institutions to simultaneously record all 12 leads at rest and during exercise at 500 samples/second.[6] This data was stored in a digitized but unprocessed state on optical discs with 400 megabyte capacity, allowing up to 80 exercise tests to be stored per disc. All optical disc recordings were processed off-line on a MSDOS computer (Intel 80386 SX, Intel, San Jose, California). After averaging, onset and offset points were determined using our own software,[6] and various QRS and ST-segment criteria were calculated. Measurements obtained included STO (J junction), ST60 (60 ms after J junction) and ST slope between these points. ST-segment depression was measured at the J junction during either exercise or recovery, whichever was greatest. Only horizontal or downsloping ST-segment depression was considered an abnormal response. From consideration of when slope was considered horizontal visually compared with computer analysis, we determined horizontal by computer measurement to be <0.7 mV/second during exercise and <0.3 mV/second during recovery. When using the computer-generated analysis of ST-segment depression for lead V_5, the cut point of ≥0.7 mm of ST-segment depression had the best combination of sensitivity and specificity, not 1.0 mm, which was the best cut point for visual interpretation of the exercise electrocardiogram. We surmised that the computer can measure ST segments more accurately than the human eye, and when evaluating ST segments visually there is a "rounding off" of values (e.g., 0.7 mm of ST-segment depression is often rounded up to 1.0 mm visually). The cut point of ≥0.8 mm maximized sensitivity and specificity for lead II. The computer onset and offset points were checked visually, and their accuracy was confirmed. Visual scanning also confirmed that the changes in lead V_5 represented changes in V_4 / V_6 and that changes in lead II represented changes in III/aVF. Only analyses at standing before exercise, maximal exercise and 4-minute supine recovery were considered.

Angina pectoris: Angina pectoris during the test was considered typical if it was exertional and relieved by rest or nitroglycerin.

Coronary angiography: A significant coronary artery stenosis was defined as ≥70% narrowing of the diameter of 1 of the major epicardial coronary arteries or its branches, or ≥50% narrowing of the left main coronary artery measured visually in ≥2 angiographic projections. Left ventricular volumes and ejection fractions were computed from the single plane contrast ventriculogram in the 30° right anterior oblique projection using the area-length method of Dodge et al.[7] Angiography was performed within an average of 15 days of the exercise test (range 1 to 65).

Statistical analysis: Univariate statistical analysis for categorical variables was performed using the chi-square test, and quantitative variables were analyzed using Student's *t* test. Chi-square analysis with Yate's correction was also used to evaluate 2-by-2 contingency tables. Differences were considered significant at a p value of ≤0.05. Confidence intervals were calculated according to Gardner and Altman.[8] Receiver-operating characteristic curves were generated with the TRUE EPISTAT software (Version 4.0, TRUE EPISTAT Service, Richardson, Texas) and were compared using the z statistic.[9-11]

RESULTS

Training set results: Table I lists the clinical and angiographic characteristics of the study groups. As expected, more patients with CAD had an abnormal response to exercise testing manifested as angina or significant ST-segment depression. Because there was no difference in β-blocker use between the 2 groups it was thought not to significantly affect the results.

Table II lists the performance characteristics of standard ST-segment analysis measured in inferior limb lead II, precordial lead V_5 and the combination of both leads together. Lead V_5 had a better combination of sensitivity and specificity than did lead II. In fact, lead V_5 alone continued to function independently as a better marker for CAD than did the combination of leads V_5 and II. Chi-square analysis with Yate's correction documented that exercise-induced ST-segment depression in lead V_5 was an excellent marker for any CAD (chi-square = 24.11; $p < 0.001$), but lead II alone (chi-square = 2.25; $p = 0.13$) and the combination of leads V_5 and II (chi-square = 3.17; $p = 0.08$) were not. The improvement in specificity (84%) of lead V_5 compared with that of lead II (44%) was also substantial by 95% confidence interval analysis for the observed difference (22 to 58%). Lead V_5 specificity (84%) was also higher than that using combined analysis of leads V_5 and II

TABLE I Clinical and Angiographic Characteristics of the Study Group

	No CAD (n = 45)	CAD (n = 63)	p Value
Age (years)	54 ± 11	62 ± 7	<0.001
β blocker	8 (18%)	14 (22%)	NS
Exercise response			
Avg. maximal HR (beats/min)	132 ± 21	124 ± 20	NS
Avg. maximal SBP (mm Hg)	172 ± 27	170 ± 28	NS
Avg. METs	8.0 ± 3.0	7.0 ± 2.0	NS
No. with angina during test	3 (7%)	16 (26%)	0.02
No. with abnormal lead II response	25 (56%)	45 (71%)	0.13
No. with abnormal lead V_5 response	7 (16%)	41 (65%)	<0.001
No. with abnormal lead II or V_5 response, or both	27 (60%)	49 (78%)	0.08
Angiography			
No CAD	45 (100%)	0 (0%)	—
1-vessel CAD	0 (0%)	32 (51%)	—
2-vessel CAD	0 (0%)	11 (17%)	—
3-vessel/LM CAD	0 (0%)	20 (32%)	—
Avg. LVEDP (mm Hg)	11 ± 4	13 ± 7	NS
Avg. LVEDVI (ml/m^2)	86 ± 34	82 ± 27	NS
Avg. LVEF (%)	69 ± 10	69 ± 11	NS

Avg. = average; CAD = coronary artery disease; HR = heart rate; LM = left main; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; METs = multiple of basal oxygen consumption = 3.5 cc of oxygen consumed/kg/min; NS = not significant; SBP = systolic blood pressure.

(40%) (95% confidence interval for observed difference 26.6 to 62.2%). Most importantly, the positive predictive value of lead II (probability of having CAD with a positive test) was only minimally higher than the pretest probability of disease.

Receiver-operating characteristic curve analysis: To compare the 2 leads over all ranges of sensitivities and specificities at multiple cut points, receiver-operating characteristic curve analysis was performed. Figure 1 is a comparison of curves for leads II and V_5. The area under the curve for lead V_5 (0.759) was significantly greater than that for lead II (0.582) ($z = 3.032$; $2p = 0.002$). More disturbingly, the area under the curve for lead II (0.582) was not significantly >0.50, which is the area under a straight line that bisects the graph ($x = y$) that represents no discrimination ($z = 1.465$; $p = 0.07$).

Test set results: To verify that the present study's results were not biased because of patient characteristics, a second validation group was selected to compare the 2 leads. This group was derived from the Hungarian Institute of Cardiology, and its patients' clinical, exercise and angiographic characteristics are listed in Table III. There was an increased use of β blockers in the group with CAD, and subsequently they had a lower peak heart rate during exercise. Table IV summarizes the performance characteristics of leads II and V_5, and both leads combined. Chi-square analysis with Yate's correction again revealed that the sensitivity and specificity of lead V_5 for identifying CAD were statistically significant (chi-square = 9.89; $p = 0.002$), but in lead II (chi-square = 0.00; $p = 1.00$) and the combination of leads V_5 and II (chi-square = 0.11; $p = 0.74$) they were

TABLE II Exercise Electrocardiogram Performance Using Leads II and V_5 for the Diagnosis of Any Coronary Artery Disease

	II	V_5	II or V_5, or Both
Sensitivity (%)	71	65	78
Specificity (%)	44	84	40
Positive predictive value/post–test probability of any CAD (%)	64	85	64
Negative predictive value (%)	53	63	56

Prevalence/pretest probability of any CAD = 58%.
CAD = coronary artery disease.

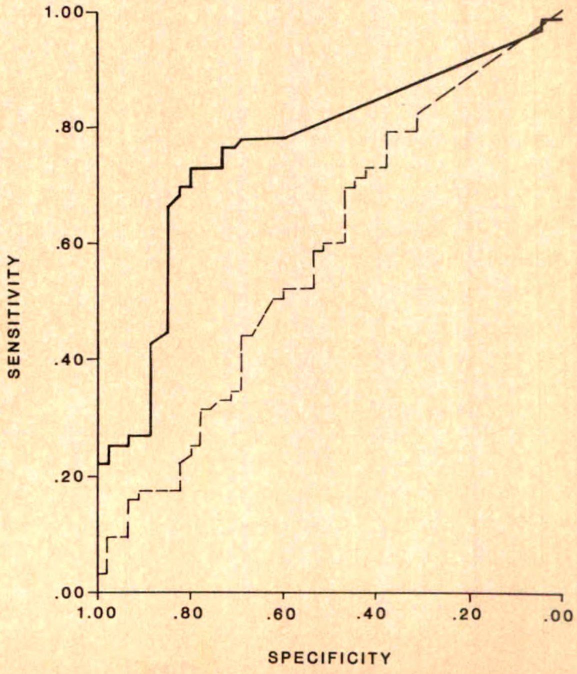

FIGURE 1. Comparison of receiver-operating characteristic curves of leads V_5 *(solid line)* and II *(dashed line)* in training population.

TABLE III Clinical and Angiographic Characteristics of the Hungarian Study Group

	No CAD (n = 31)	CAD (n = 34)	p Value
Age (years)	46 ± 7	50 ± 8	0.04
β blocker	2 (6%)	10 (29%)	0.02
Exercise response			
Avg. maximal HR (beats/min)	142 ± 24	125 ± 21	<0.01
Avg. maximal SBP (mm Hg)	189 ± 26	185 ± 28	NS
Avg. METs	7.8 ± 2.4	7.0 ± 1.5	NS
No. with angina during test	1 (3%)	9 (26%)	0.01
No. with abnormal lead II response	16 (52%)	17 (50%)	NS
No. with abnormal lead V_5 response	4 (12%)	18 (53%)	0.002
No. with abnormal lead II or V_5 response, or both	16 (52%)	20 (59%)	NS
Angiography			
No CAD	31 (100%)	0 (0%)	—
1-vessel CAD	0 (0%)	17 (50%)	—
2-vessel CAD	0 (0%)	7 (21%)	—
3-vessel/LM CAD	0 (0%)	10 (29%)	—

Abbreviations as in Table I.

not. Furthermore, 95% confidence interval analysis for the observed difference between the specificities of leads V_5 and II was substantial (17.5 to 59.9%). The specificity was much better with V_5 alone (87%) than with lead V_5 combined with lead II (48%) by 95% confidence interval analysis for the observed difference (17.5 to 59.9%), as well. The post-test probability of CAD for lead II was exactly the same as the pretest probability (52%), revealing that the lead II ST changes added nothing to the diagnosis of CAD. Receiver-operating characteristic curve analysis revealed that measurement of ST-segment depression in lead V_5 (area = 0.768) was superior to that in lead II (area = 0.521) ($z = 3.531$; $2p < 0.001$) (Figure 2). The area under the curve for exercise-induced ST-segment depression in lead II (area = 0.521) again was not significantly >0.50 ($z = 0.287$; $p = 0.39$).

DISCUSSION

Major findings of the present study: Exercise-induced ST-segment depression in inferior limb lead II was a notoriously poor marker for CAD, in and of itself. Precordial lead V_5 alone consistently outperformed lead II and the combination of leads V_5 and II, because lead II had such a high false-positive rate.

TABLE IV Exercise Electrocardiogram Performance Using Leads II and V_5 for the Diagnosis of Any Coronary Artery Disease in the Hungarian Validation Group

	II	V_5	II or V_5, or Both
Sensitivity (%)	50	53	59
Specificity (%)	48	87	48
Positive predictive value/ post–test probability of any CAD (%)	52	82	56
Negative predictive value (%)	47	63	52

Prevalence/pretest probability of any CAD = 52%.
CAD = coronary artery disease.

Comparisons with other studies: Since the time of Einthoven investigators have searched for electrocardiographic criteria that were sensitive for ischemia, and it has been known since the early days of exercise testing that the lateral precordial leads are the optimal markers for CAD. Blackburn and Katigbak[12] found that lead V_5 alone detected 89% of ischemic ST-segment responses. Miller et al[13] evaluated 44 patients who had both abnormal exercise tests and perfusion defects on thallium-201 scintigraphy. They found that monitoring the inferior leads rarely provided additional diagnostic information. Mason et al[14] found that in 67 patients with

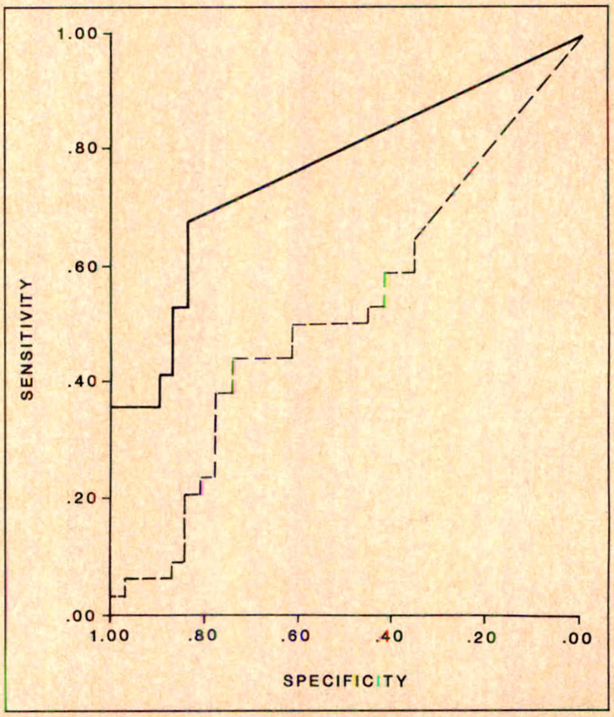

FIGURE 2. Comparison of receiver-operating characteristic curves of leads V_5 *(solid line)* and II *(dashed line)* in Hungarian validation cohort.

angina who underwent exercise testing, 19 had an abnormal electrocardiographic response in 1 lead only, and only 2 of these were isolated to lead II. Seven patients in the present study had ST-segment depression in lead II only without concomitant electrocardiographic changes in lead V_5, and only 3 of these responses were true positives. Sketch et al[15] studied 203 men with both exercise testing and coronary angiography, and found that lead II had a sensitivity of only 34%. In evaluating body surface potential distributions in 50 subjects (25 with CAD), Simoons and Block[16] concluded that a single bipolar V_5 lead was adequate to diagnose ischemia in patients without prior myocardial infarction and normal electrocardiograms at rest. Riff and Carleton[17] studied patients in atrioventricular dissociation and demonstrated that atrial repolarization can cause J-point depression in the inferior leads, which may produce the false-positive responses.

It should be remembered that even though the present study shows that inferior lead ST-segment depression is not a reliable, independent marker for the diagnosis of CAD it is helpful for diagnosing severe ischemia, because multiple lead involvement has been associated with multivessel[18] and left main[19] CAD. However, concomitant exercise-induced inferior lead ST-segment depression may be an indicator of multivessel ischemia, but it does not localize right coronary involvement.[20]

Study limitations: The present study did not evaluate all the inferior leads simultaneously by computer, and this may have placed these leads at a selective disadvantage. However, as mentioned previously, leads III and aVF were visually scanned to verify that lead II was representative of changes in them as well. Lead II was chosen as the representative inferior lead because in our laboratory it is the inferior lead that is most stable for recording during exercise. The increased use of β blockers in the Hungarian group with CAD may have caused more false-negative exercise tests. Our results must be viewed in the context of the study's selection bias (post-test referral bias), which compromises its specificity.[21-26] The exclusion of women from the study confines our conclusions to men. Finally, retrospective analyses must be confirmed by comparisons with other databases, prospective studies, or both.

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Comparison of One-, Six- and 24-Hour Ambulatory Electrocardiographic Monitoring for Ventricular Arrhythmia as a Predictor of Mortality in Survivors of Acute Myocardial Infarction

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on behalf of the CAMIAT Pilot Study Group*

To compare 1-, 6- and 24-hour ambulatory electrocardiograms for prediction of mortality after acute myocardial infarction (AMI), all patients with AMI hospitalized in Hamilton, Ontario during 1 year were identified. There were 683 patients discharged alive after AMI. One-, 6- and 24-hour ambulatory electrocardiographic results were available in 565 patients, and follow-up mortality data at 1 year was available in 560. Mean age of the patients was 64 years; 160 (29%) had previous AMI and 105 (19%) had had congestive heart failure. One hundred and fifty-two patients (27%) were receiving β blockers, and 31 (6%) were receiving antiarrhythmic drugs. Regression modeling of survival times up to 1 year showed that all 3 durations of recording were univariate predictors of mortality. Using >10 ventricular premature complexes/hour as the criterion of a positive test, neither the 6- nor 24-hour data contained statistically significant residual explanatory power after the 1-hour data were accounted for by the model. The longer durations of recording increased sensitivity at a cost of decreased specificity. The positive and negative predictive values of the 3 durations of recording were virtually identical. The presence of ventricular tachycardia was not a significant predictor of mortality in this population. There appears to be no benefit to ambulatory electrocardiographic recordings >1 hour when they are to be used for prediction of 1-year mortality after AMI.

(Am J Cardiol 1992;69:308–313)

The ambulatory electrocardiogram is useful for risk stratification in surviving patients of acute myocardial infarction (AMI). Cohort follow-up studies have consistently shown that frequent ventricular premature complexes on the ambulatory electrocardiogram significantly and independently increase the risk of death 1 to 5 years after AMI.[1–13]

Although the results of the Cardiac Arrhythmia Suppression Trial[14] cautioned against the use of encainide and flecainide in AMI survivors, there continues to be great interest in the identification of patients at high risk of death after AMI who may benefit from other types of antiarrhythmic therapy.[15] Although recent studies used 24-hour recording periods to characterize ventricular arrhythmia,[11–13] the first studies to document the prognostic significance of ventricular arrhythmia used much shorter periods (<1 minute to 6 hours).[1–10,16] In 1988, Davis et al[17,18] compared the predictive value of the 24-hour ambulatory electrocardiogram to shorter durations of recording in 1,336 placebo patients in the Beta Blocker Heart Attack Trial (BHAT). They concluded that increasing the duration of ambulatory monitoring >4 hours does not substantially improve the performance of the test for predicting mortality or deciding whether to use antiarrhythmic treatment. The generalizability of their conclusions to the entire postinfarction population is unclear, because the BHAT participants are a selected sample of this population. The 24-hour recording period remains standard in most medical centers; it is more expensive and inconvenient to the patient than is 1- or 6-hour recording, and may not improve mortality prediction. The purpose of the present study was to determine the relative values of 1-, 6- and 24-hour ambulatory electrocardiographic recordings in a cohort of unselected patients who survived the hospital course of AMI.

METHODS

From May 12, 1986, to May 11, 1987, all patients hospitalized with AMI in the geographic area of Hamilton, Ontario (population 390,000 in 1986) were identified. There are 5 coronary care units in this city, and the general policy of each is to admit any patient with possible AMI without age restriction. One of 2 nurse

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practitioners visited each coronary care unit in Hamilton daily during the study to identify all patients with AMI. The diagnosis of AMI was assigned to a patient when ≥ 2 of the following criteria were present: (1) characteristic ischemic pain in the precordium or associated referral areas lasting ≥ 15 minutes after the patient was at physical and emotional rest; (2) elevation of ≥ 2 of aspartate aminotransferase, creatine kinase or lactate dehydrogenase to greater than twice the upper limit of normal for the given hospital, or creatine kinase MB fraction to $>5\%$ of total creatine kinase; (3) development of new 40 ms Q waves in ≥ 2 adjacent electrocardiographic leads, of dominant R waves in lead V_1 or of evidence of non-Q-wave infarction (ST depression ≥ 1 mm, or T-wave inversion ≥ 3 mm in ≥ 2 adjacent electrocardiographic leads lasting ≥ 7 days); and (4) death in the hospital within 2 hours, with any 1 of the above criteria positive.

Patients with cardiac arrest out-of-hospital or in the emergency room who never recovered consciousness, and those transferred to Hamilton hospitals from outside hospitals were not included in the analysis. Patients were registered in the data base at the occurrence of their first AMI during the time period of this study, and mortality follow-up was related to this AMI. Details of demographic, clinical and laboratory data were recorded on standard forms. Patients who survived to their sixth day after admission to the coronary care unit became eligible for 24-hour ambulatory electrocardiographic monitoring. However, the population of the present report included only patients who were discharged alive from the hospital. The ambulatory electrocardiogram was attached 6 to 30 days after the onset of AMI between 0900 and 1700 hours as part of screening for a separate randomized clinical trial. The tape was analyzed only if there was ≥ 18 hours of electrocardiographic recording, free of major artifact. Ventricular tachycardia runs were defined as ≥ 3 consecutive ventricular premature complexes at a mean RR interval ≤ 600 ms. The ambulatory electrocardiographic analysis system used was validated against annotated American Heart Association tapes with accuracy $>95\%$. Patients stopped receiving antiarrhythmic drugs for ≥ 5 drug half-lives before the recording of the ambulatory electrocardiogram, if their physicians agreed. However, 6% of patients were receiving antiarrhythmic drugs at the time of the recording. Each tape was also analyzed to obtain the ventricular premature complex and ventricular tachycardia run count for the first hour and the first 6 hours of recording.

Between September 1988 and January 1989, the mortality status of each patient was determined as of 1 year from the date of admission to the hospital for AMI. Hospital records were first searched to determine if a hospital contact had occurred ≥ 1 year after AMI. If not, then the patient's family doctor was contacted to determine his/her awareness of the patient's mortality status. If the physician did not know the 1-year mortality status of the patient, the patient's family was contacted by telephone to obtain the relevant information. The remaining names were submitted to the Provincial Death Registry to determine whether death certificates were recorded in the Province of Ontario.

TABLE I Patient Characteristics (n = 560)

Age (years)	64 ± 13
Men/women	390 (70%)/170 (30%)
Peak creatine kinase (U/L)	1,260 ± 1,256
Anterior AMI	245 (44%)
Acute ventricular fibrillation	24 (4%)
Initial heart rate (beats/min)	81 ± 22
Previous AMI	160 (29%)
Shock after AMI	29 (5%)
CHF after AMI	105 (19%)
β-blocker therapy	152 (27%)
Digoxin therapy	91 (16%)
Antiarrhythmic drug therapy	31 (6%)

AMI = acute myocardial infarction; CHF = congestive heart failure.

The BMDP computerized statistical software package was used to model survival using stepwise multivariate proportional hazards regression. All data were censored at 1 year. After assessing the univariate predictive powers of the 1-, 6- and 24-hour ambulatory electrocardiographic results, the 1-hour results were forced into the model, and the residual predictive powers of the 6- and 24-hour electrocardiograms were assessed. Then, the results of the 6-hour recording were forced into the model to determine the residual predictive power of the 24-hour recording. This analysis was performed separately for both ventricular premature complexes and ventricular tachycardia runs. Runs were treated as a dichotomous variable (either present or absent). Ventricular premature complexes counts were dichotomized at >10/hour.

The following definitions were used: sensitivity = patient died, probability of arrhythmia being present; specificity = patient lived, probability of arrhythmia being absent; positive predictive value = arrhythmia present, probability that patient died; and negative predictive value = arrhythmia absent, probability that patient survived. The study was approved by the institutional review board of each participating hospital.

RESULTS

Patients who were discharged alive from the hospital after AMI constitute the source population for the present study. From May 12, 1986, to May 11, 1987, there were 682 patients admitted with AMI who were discharged alive. An ambulatory electrocardiogram with 1-, 6- and 24-hour counts was available in 565 patients (83%), and the 1-year survival status was known in all but 5. The demographic and clinical characteristics of the patient population are listed in Table I.

The results of multivariate regression modeling are listed in Table II. Using >10 ventricular premature complexes/hour as the criterion of a positive test, all 3 recording durations were strong univariate predictors of survival. However, after the 1-hour data were entered into the model, subsequent entry of either the 6- or 24-hour data did not significantly improve the fit of the

TABLE II Results of Stepwise Multivariate Modeling of Survival

> 10 VPC/Hour				
Hours of Recording	Pts. with > 10 VPC/Hour	Risk Ratio of > 10 vs ≤ 10 VPC/Hour	Univariate Chi-Square (p value)	One-Hour Results in Model, Residual Chi-Square (p value)
1	80 (14%)	2.73	12.00 (0.005)	
6	85 (15%)	2.84	13.33 (0.003)	1.48 (0.223)
24	94 (17%)	2.73	12.85 (0.003)	1.71 (0.191)

Ventricular Tachycardia				
Hours of Recording	Patients with VT	Risk Ratio of VT vs No VT	Univariate Chi-Square (p value)	One-Hour Results in Model, Residual Chi-Square (p value)
1	12 (2%)	2.31	1.58 (0.208)	
6	19 (3%)	2.65	3.37 (0.067)	1.80 (0.179)
24	42 (8%)	2.11	3.61 (0.057)	2.11 (0.146)

Univariate risk ratio of > 10 VPC/hr is the ratio of mortality rate of patients with > 10 VPC/hr to that of those with ≤ 10 VPC/hr.

Chi-square and p value are the statistic and probability associated with the improvement of the fit of the proportional hazards model to survival data when an explanatory variable is entered into the model. This statistic is given for each recording duration with no other variables in the model (univariate) and with the 1-hour data already accounted for by the model.

VPC = ventricular premature complex; VT = ventricular tachycardia.

TABLE III Sensitivity and Specificity of Ambulatory Electrocardiogram

	Sensitivity			Specificity		
VPC/Hour	One Hour	Six Hours	24 Hours	One Hour	Six Hours	24 Hours
>0	62	82	83	64	42	23
>1	52	67	62	73	70	68
>3	44	47	55	80	79	77
>6	36	38	44	84	84	82
>10	30	32	33	87	87	85
>30	21	21	24	92	92	92
>60	15	14	15	94	95	94

VPC/Hour = ventricular premature complexes/hour; cut point at which results were dichotomized into positive and negative tests.

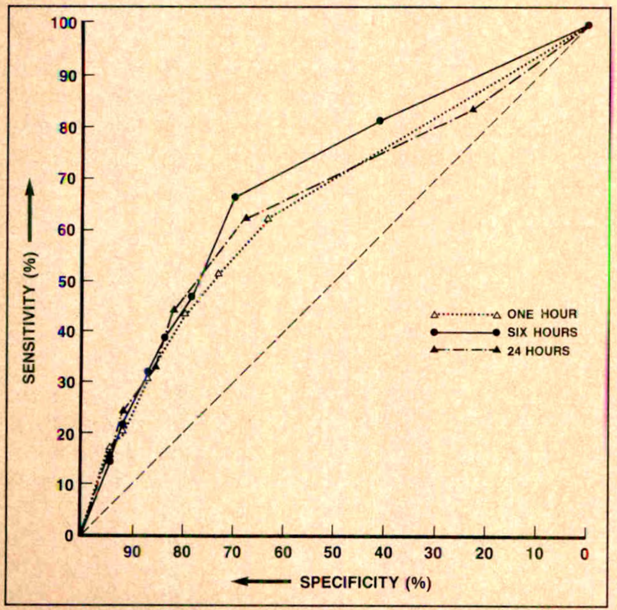
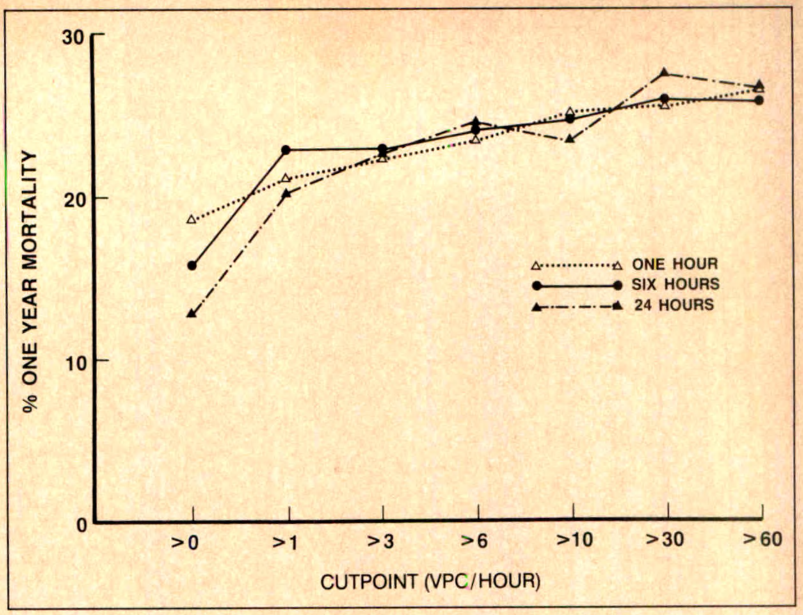


FIGURE 1. Receiver-operator plots of 1-, 6- and 24-hour recording durations showing relation between sensitivity and specificity for prediction of 1-year mortality. *Points* on each curve are derived from relation of sensitivity and specificity for each cut point of ventricular premature complex frequency from >0 to >60/hour.

model to the survival data. Using presence of ventricular tachycardia as the criterion of a positive test, none of the 3 durations of recording was a statistically significant univariate predictor of survival, although there was a strong trend for the 6- and 24-hour results.

Table III shows the sensitivity and specificity of the ambulatory electrocardiogram to detect patients who will die within 1 year of hospital admission for AMI. The ambulatory electrocardiographic results were dichotomized at several cut points of ventricular premature complex frequency (0 and >0, ≤ and >1, ≤ and >3, and so forth). The sensitivity (probability of ventricular premature complex frequency above the cut point in patients who subsequently die) and specificity (probability of ventricular premature complex frequency below the cut point in patients who survive) of the 1-, 6- and 24-hour recordings were tabulated. At all cut points, sensitivity increases and specificity decreases as the duration of recording is increased from 1 to 6 to 24 hours. Therefore, as recording duration lengthens, the ambulatory electrocardiogram identifies more of the patients who will die over the first year (increasing sensitivity), but also wrongly predicts death in an increasing number of patients (decreasing specificity). The receiver-operator curve expresses the overall performance of a test by plotting sensitivity against specificity using sev-

FIGURE 2. Positive predictive values of 1-, 6- and 24-hour recording durations over range of cut points of ventricular premature complex (VPC) frequency at which ambulatory electrocardiographic results are dichotomized into positive and negative.



eral different cut points. As the overall performance of a given test improves, the receiver-operator curve will diverge from unity. In Figure 1, the receiver-operator plots for 3 recording durations of ambulatory electrocardiographic recording are seen to be very similar.

Another way to evaluate the performance of a predictive test is to consider the mortality rate of patients with a positive test and the survival rate of those with a negative test (positive and negative predictive values). These are shown graphically in Figures 2 and 3 using several different cut points for dichotomizing the results into positive and negative. Except for a small divergence at the lowest cut points, the 3 durations of recording perform in a very similar manner.

Figure 4 depicts the relation between 1-year mortality and frequency of ventricular premature complexes. For all 3 recording durations there is a steady increase in 1-year mortality as frequency of ventricular premature complexes increases, and the 3 curves are essentially the same.

DISCUSSION

The earliest studies to evaluate the predictive value of ventricular arrhythmia in surviving patients of AMI used short durations of electrocardiographic recording.[1-10,16] In the study of the Coronary Drug Project Research Group,[16] 2,035 surviving patients of AMI had one 12-lead electrocardiogram, and during 3-year follow-up there was 21.4% mortality in those with any ventricular premature complexes compared with 11.2% in those without ($p < 0.01$). Ruberman et al[7-10] obtained a 1-hour electrocardiogram in 1,739 patients, most of whom had had AMI within the previous 3 months. During a mean follow-up of 2 years patients with complex ventricular premature complexes (frequent, repetitive or multiform) had a 28.3% age-adjusted 3-year mortality rate compared with 12.1% for those with no ventricular premature complexes. Using 6-hour recordings, Moss et al[1-6] showed that ventricular premature complex frequency and complexity were independent predictors of total mortality and sudden death in surviving patients of AMI.

Only 1 previous study evaluated the relative values of different durations of ambulatory electrocardiographic recording for risk stratification. Using data collected as part of the BHAT Davis et al[17] evaluated the baseline ambulatory electrocardiogram of 1,336 patients who survived AMI and were randomized to placebo. They compared the power of a random hour and of the first 1, 2, 4, 6, 12 and 24 hours of ambulatory electrocardiographic recording to predict survival during an average 25-month follow-up. The longer durations of recording had increased sensitivity for the prediction of

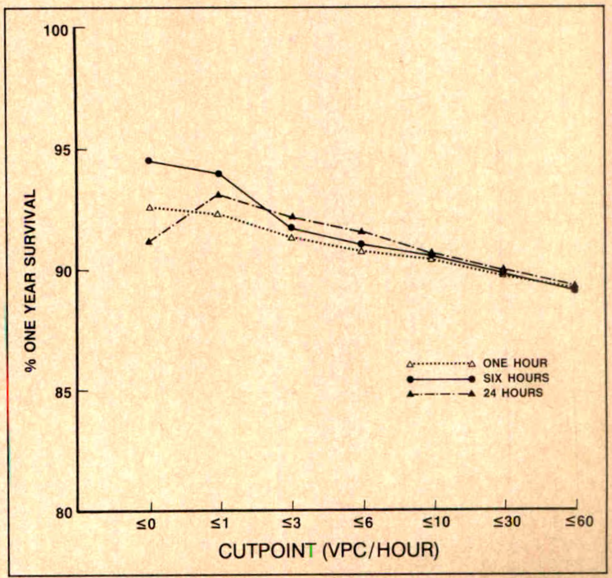


FIGURE 3. Negative predictive values of 1-, 6- and 24-hour recording durations over range of cut points of ventricular premature complexes (VPC) frequency at which ambulatory electrocardiographic results are dichotomized into positive and negative.

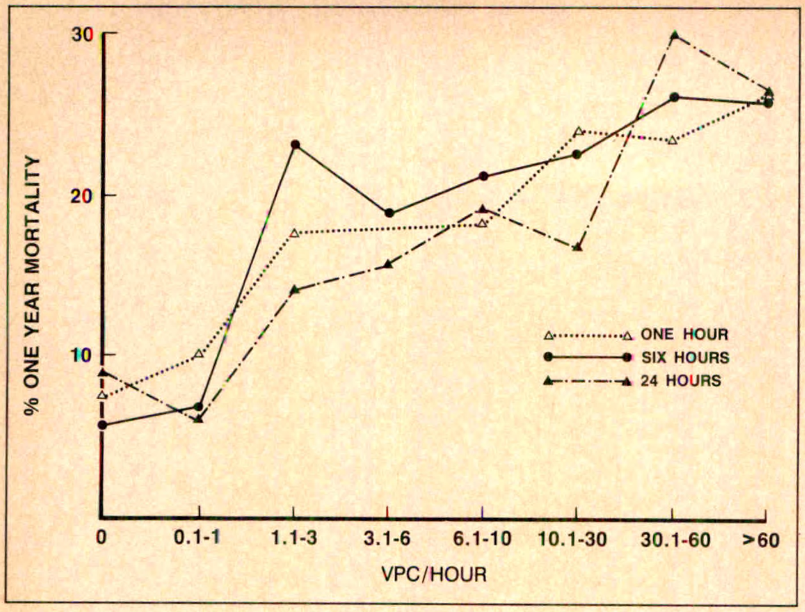


FIGURE 4. Relation between 1-year mortality and frequency of ventricular premature complexes (VPC) for 1-, 6- and 24-hour recording durations.

death, but this was offset by a reduction in specificity. Overall, there was little advantage to recordings >1 hour. In a subsequent analysis of these data,[18] a decision theoretic approach was explored to determine the most useful duration of monitoring for making a treatment decision based on postulated risk-benefit ratios of antiarrhythmic therapy. This analysis indicated that recording periods >4 hours would not be useful for deciding whether to use antiarrhythmic therapy. The BHAT participants were a highly selected sample of the postinfarction population with a relatively low incidence of congestive heart failure, and a lower mean age than that of the overall population of surviving patients of AMI. Therefore, the generalizability of the results of this study is uncertain. However, the present study includes a very high proportion of all hospitalized patients who survived AMI in a defined community who were available for ambulatory monitoring.

The present study confirms the results of Davis et al[17,18] and extends these results to the postinfarction population at large. All 3 durations of recording in the present study are strong univariate predictors of total mortality. Virtually all of the predictive information in the 24-hour ambulatory electrocardiogram is contained in the first hour of recording. Although the sensitivity of the test to detect those who will die is somewhat improved by increasing the duration of recording, this is offset by a corresponding reduction in specificity. The optimal balance between sensitivity and specificity depends on how the test is to be used. When treatments have a low risk-benefit ratio, the use of a test with higher sensitivity and lower specificity to detect treatment candidates is indicated in order to identify a greater percentage of potential responders. The fact that due to low specificity, more patients who would not benefit from treatment would be exposed to treatment, would be of lesser consequence. At present, the best evidence indicates that antiarrhythmic therapy has a relatively high-risk–benefit ratio.[14] In this situation it would appear that short durations of recording are most appropriate, because they optimize specificity and result in fewer low-risk patients being exposed to treatment.

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APPENDIX

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Clinical Angiographic and Histologic Correlates of Ectasia After Directional Coronary Atherectomy

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Directional coronary atherectomy can cause ectasia (final area stenosis <0%), presumably due to an excision deeper than the angiographically "normal" arterial lumen. In a multicenter series in which quantitative coronary arteriography was performed after directional atherectomy in 382 lesions (372 patients), ectasia after atherectomy occurred in 50 (13%) lesions. By univariate analysis, ectasia was seen more often within the circumflex coronary artery ($p = 0.008$), in complex, probably thrombus-containing lesions ($p = 0.015$), and with higher device:artery ratios ($p < 0.001$). Ectasia occurred less often in lesions within the right coronary artery ($p = 0.008$). Histologic analysis demonstrated adventitia or media, or both, in all patients with angiographic ectasia. Repeat angiography was performed in 188 of 271 eligible patients (69%) 6.1 ± 2.4 months after atherectomy. Restenosis, defined as a follow-up area stenosis ≥75%, was present in 50% of patients without procedural ectasia and in 70% of patients with marked ectasia (residual area stenosis <−20%; $p = 0.12$). It is concluded that excision beyond the normal arterial lumen may occur after directional coronary atherectomy, related, in part, to angiographic and procedural features noted at the time of atherectomy. Restenosis tends to occur more often in patients with marked ectasia after coronary atherectomy.

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Because of limitations of standard balloon angioplasty, including abrupt vessel closure and delayed restenosis, alternative methods of nonsurgical coronary revascularization have been used.[1–3] One such technique is directional coronary atherectomy, which dilates and selectively excises the obstructive atheroma.[4,5] Directional atherectomy has been shown to be particularly useful in lesions deemed high risk for standard coronary angioplasty, such as those with irregularity, ulceration or those containing thrombus.[6,7]

Despite the potential advantages of directional coronary atherectomy, the optimal depth of resection by this method has not been determined. Whereas deeper excisions into the normal vessel wall may be performed without important immediate clinical sequelae,[8] higher restenosis rates after directional atherectomy have been reported when the depth of resection includes media and adventitia, particularly in lesions within saphenous vein grafts.[9] Often, the direction and depth of cut is operator-dependent, with some clinicians advocating an aggressive approach to atheroma resection in an effort to reduce late restenosis,[10] while others resect less atheroma because of the potential risk of vessel perforation.[1]

Whether excision beyond the "normal" arterial lumen, demonstrated angiographically as ectasia, results in an increased incidence of early or late clinical sequelae has not been previously studied. Therefore, to characterize the incidence, predisposing factors, histologic findings, and clinical outcome of ectasia after directional coronary atherectomy, clinical case report forms were reviewed and cineangiograms were analyzed using qualitative morphologic and quantitative angiographic methods for 382 directional atherectomy procedures performed at 6 clinical sites.

METHODS

Patient population: Between January 1988 and July 1990, directional coronary atherectomy was performed in 400 procedures at 6 clinical centers. Proximal lesions or lesions with irregularity, ulceration, or eccentricity in coronary arteries ≥2.5 mm were deemed suitable for directional coronary atherectomy. Before the atherectomy procedure, all patients gave informed consent, approved by the respective institutional review boards. Completed clinical case report forms and cineangiograms suitable for quantitative coronary analysis were obtained in 382 procedures.

From the Departments of Internal Medicine (Cardiology Divisions) of the University of Michigan Medical Center, Ann Arbor, Michigan, the Mayo Clinic, Rochester, Minnesota, the Cleveland Clinic Foundation, Cleveland, Ohio, Emory University, Atlanta, Georgia, St. Vincent's Hospital, Indianapolis, Indiana, the Christ Hospital, Cincinnati, Ohio, and the Mallory Institute of Pathology, Cardiovascular Research Laboratory, Boston, Massachusetts. Manuscript received August 8, 1991; revised manuscript received September 27, 1991, and accepted September 29.

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Atherectomy procedure: Directional coronary atherectomy was performed with the Simpson AtheroCath™ (Devices for Vascular Intervention, Inc., Redwood City, California) using previously described methods.[1] In general, the depth of resection was determined primarily by the principal investigator. After each series of passes, repeat arteriography was performed to ascertain the amount of residual obstruction. Before November 1989, most investigators attempted to resect all angiographically apparent atheroma. Thereafter, because of concern about a rarely reported perforation,[1] a less aggressive approach to complete atheroma resection was taken by some investigators. Successful atherectomy was defined as a residual area stenosis $<75\%$, tissue retrieval, and the absence of in-hospital ischemic complications.

Clinical and procedural features: Case report forms were reviewed for age, gender, angina status, the presence of diabetes mellitus, multivessel disease and a history of restenosis. Procedural variables, including adjunctive coronary angioplasty, atherectomy device size, number of passes, and number of specimens obtained, were also recorded. The occurrence of major postprocedural ischemic complications, such as abrupt closure, myocardial infarction, emergency coronary bypass surgery and death, was noted.

Qualitative morphologic analysis: Cineangiograms were collected at the University of Michigan Core Angiographic Laboratory and analyzed by an observer unaware of the clinical outcome. Lesions were visualized in multiple projections and scored according to lesion location, eccentricity, proximal tortuosity, diffuse proximal disease, lesion length ≥ 10 mm, bend $\geq 45°$, irregularity, presence of calcific deposits, or bifurcation location using the criteria developed by Ellis and co-workers.[11] Complex, probably thrombus-containing, stenoses were defined as the presence of either an easily recognized filling defect or gross luminal irregularities within the lesion. The device:artery ratio was measured by calipers and defined as the ratio of the atherectomy device and the normal adjacent coronary artery for the largest device that crossed the stenosis.

Quantitative coronary angiography: Quantitative coronary analysis was performed using cineangiograms obtained before and immediately after directional coronary atherectomy. Selected end-diastolic cine frames from orthogonal projections demonstrating the stenosis in its least foreshortened projection were digitized using a cine-video converter. A computer-assisted edge-detection algorithm was applied to the digitized images[12] and, using the guiding catheter as the reference standard, absolute coronary dimensions and percent stenoses were obtained. The normal segment was measured in a region without luminal irregularities 5 to 10 mm proximal to and 5 to 10 mm distal to the stenosis. The identical region of minimal luminal diameter before coronary atherectomy was used to define the region of measurement of the luminal diameter immediately after atherectomy. Normal and minimal cross-sectional areas were determined based on the geometry of an ellipse.[13] Ectasia was defined as $<0\%$ residual area stenosis after coronary atherectomy and marked ectasia was defined as $<-20\%$ area stenosis in the region of atherectomy (Figures 1 and 2). At time of follow-up arteriography, restenosis was defined as an area stenosis $\geq 75\%$ using

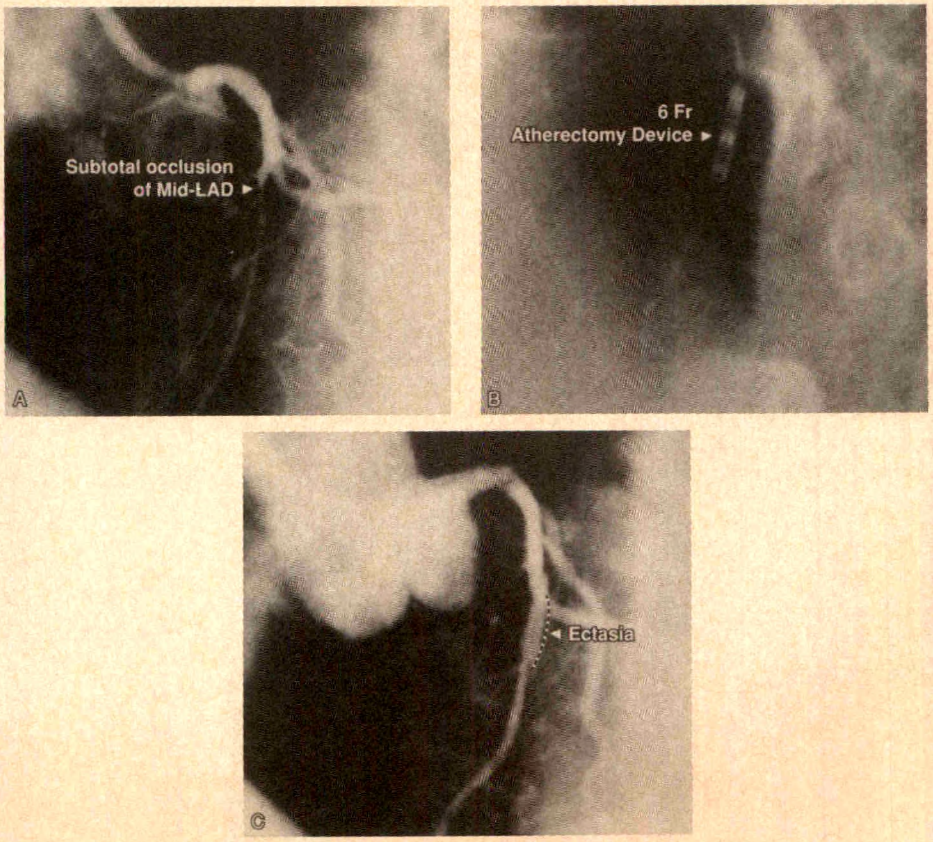

FIGURE 1. A subtotal occlusion of the left anterior descending artery (LAD) is noted in the left anterior oblique projection *(panel A)*. A 6Fr directional atherectomy device is positioned across the stenosis and 4 passes are performed *(panel B)*. After atherectomy, ectasia is noted within the midleft anterior descending artery *(panel C)*. Subacute abrupt vessel closure developed 4 days after atherectomy and was successfully managed with coronary angioplasty.

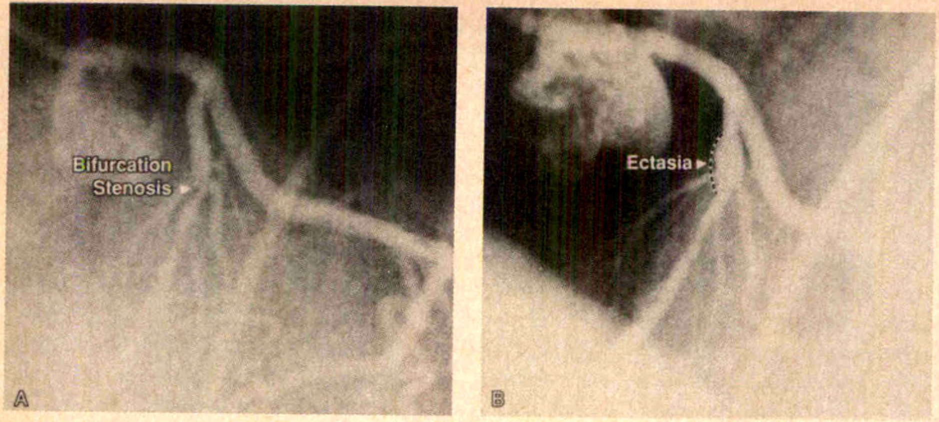

FIGURE 2. A complex stenosis of the midleft anterior descending artery is noted *(panel A)*. After atherectomy with a 7Fr device, marked ectasia is seen *(panel B)*. At follow-up arteriography 6 months later, no significant change in the luminal dimensions was noted.

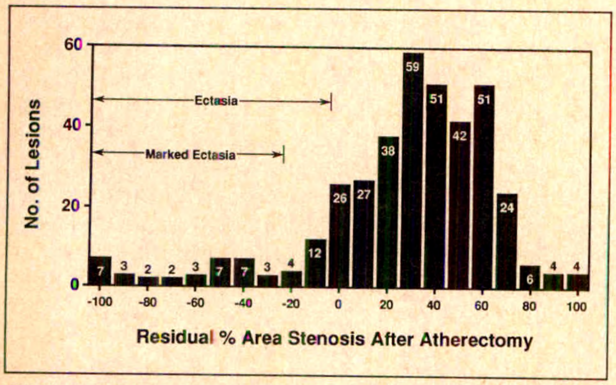

FIGURE 3. Distribution of residual percent area stenosis after atherectomy. Ectasia, defined as <0% residual stenosis, was present in 50 lesions (13%), and marked ectasia, defined as <−20% residual stenosis, was present in 34 lesions (9%).

similar quantitative methods. Intimal hyperplasia was defined as the loss of minimal lesion cross-sectional area (mm^2) during the period of follow-up. Because of institutional requirements, follow-up films were not available for analysis from 1 participating institution; therefore, these lesions were not included in follow-up analysis.

Histologic analysis: Pathologic examination of specimens retrieved from 76 lesions was available from 1 of the 6 participating institutions. After removal from the atherectomy device, specimens were placed in either formalin or glutaraldehyde/formalin fixative and evaluated by a histopathologist unaware of the clinical and angiographic results using previously described methods.[14] Atherosclerotic plaque, including fibrocellular, sclerotic and lipid-containing components, was identified using a hematoxylin-eosin stain. Normal vessel wall beyond the internal elastic lamina, containing media and adventitia, was identified using a Van Gieson elastin stain.

Statistical analysis: All continuous variables were expressed as mean ± SD and dichotomous variables were expressed as frequencies. Nonparametric analysis was used to evaluate differences in continuous variables and chi-square analysis was used to evaluate differences in dichotomized variables. A $p < 0.05$ was considered significant.

RESULTS

Incidence of ectasia after directional atherectomy: During the study period, successful directional atherectomy was performed in 317 of 382 procedures (83%). The clinical, angiographic and procedural factors correlating with the procedural success and complication rates have been reported elsewhere.[7,15] With use of quantitative angiographic methods, ectasia developed in 50 lesions (13%) and marked ectasia, defined as a residual area stenosis <−20%, occurred in 34 lesions (9%) (Figure 3). No clinical characteristics were correlated with the development of ectasia after directional atherectomy (Table I). However, using univariate analysis, ectasia was seen more often in lesions within the circumflex coronary artery and in complex, probably thrombus-containing lesions (Table II). Despite the varying criteria for tissue resection during the study period, no differences were noted in the incidence of ectasia between early (≤20 procedures) and later (>20 procedures) experience (11 vs 14%, respectively; p = not significant). Notably, ectasia occurred more often with larger device:artery ratios (Table III), but was not related to any other procedural factors. Coronary perforation developed in 2 (0.6%) procedures, but was not re-

TABLE I Clinical Correlates of Ectasia After Directional Atherectomy

Features	Ectasia— No. (%)	No Ectasia— No. (%)	Likelihood Ratio	Univariate p Value
Age (years)	59 ± 10	59 ± 11	—	NS
Male gender	40 (80)	259 (78)	1.02	NS
Unstable angina	27 (61)	151 (49)	1.63	0.14
Diabetes mellitus	7 (18)	39 (14)	1.39	NS
History of restenosis	19 (44)	146 (49)	0.83	NS
Multivessel disease	19 (45)	141 (47)	0.93	NS

NS = not significant.

lated to the presence of angiographic ectasia. Ischemic complications were relatively infrequent after directional atherectomy, and were not related to the presence of angiographic ectasia (Table IV).

Histologic analysis of lesions with angiographic ectasia: In lesions with histologic analysis, normal vessel wall constituents were obtained in all 11 patients with angiographic ectasia (Figure 4). In the 65 lesions without angiographic ectasia, media was obtained in 37 (53%) and adventitia was obtained in 19 (29%) lesions.

Restenosis after angiographic ectasia: Repeat coronary arteriography was performed 6.1 ± 2.4 months after directional atherectomy in 188 of 271 eligible patients (69%). Restenosis developed in 80 of 160 lesions (50%) without ectasia, in 17 of 28 lesions (61%) with ectasia, and in 13 of 19 lesions (68%) with marked ectasia ($p = 0.12$) (Table IV). Notably, intimal hyperplasia was significantly greater in lesions with angiographic ectasia immediately after directional atherectomy.

DISCUSSION

In contrast to balloon angioplasty, which exerts its principal geometric effect by splitting and tearing the atherosclerotic segment,[16,17] pathologic study has suggested that directional coronary atherectomy results in improved coronary dimensions by selectively excising

TABLE II Angiographic Correlates of Ectasia After Directional Atherectomy

Features	Ectasia— No. (%)	No Ectasia— No. (%)	Likelihood Ratio	Univariate p Value
Artery				
Left main	0 (0)	3 (1)	*	NS
LAD	28 (56)	186 (57)	0.97	NS
RCA	5 (10)	87 (27)	0.31	0.011
LCX	7 (14)	15 (5)	3.39	0.008
SVG	10 (20)	40 (11)	2.05	0.062
Lesion location				
Ostial	3 (8)	31 (11)	0.67	NS
Proximal	18 (45)	132 (46)	0.97	NS
Mid/distal	19 (48)	125 (43)	1.18	NS
Lesion morphology				
Eccentric	27 (56)	189 (59)	0.88	NS
Tortuosity	1 (2)	15 (5)	0.44	NS
Diffuse disease	4 (8)	45 (14)	0.63	NS
Length ≥ 10 mm	5 (10)	35 (11)	0.93	NS
Bend ≥ 45°	3 (6)	30 (9)	0.63	NS
Irregularity	8 (16)	56 (17)	0.95	NS
Calcification	5 (10)	36 (11)	0.91	NS
Bifurcation	6 (12)	33 (10)	1.23	NS
Complex, thrombus containing	8 (16)	21 (6)	2.85	0.015
Before atherectomy				
Normal area (mm^2)	8.8 ± 3.2	9.7 ± 4.0	—	0.07
Stenotic area (mm^2)	1.2 ± 1.0	1.2 ± 1.0	—	NS
% Area stenosis	88 ± 9	86 ± 10	—	NS
After atherectomy				
Normal area (mm^2)	8.4 ± 3.4	10.0 ± 3.9	—	0.003
Stenotic area (mm^2)	12.6 ± 6.3	5.6 ± 3.1	—	<0.001
% Area stenosis	−0.5 ± 0.5	0.4 ± 0.2	—	<0.001

*Not done due to no observations in ectasia group.
LAD = left anterior descending artery; LCX = left circumflex; NS = not significant; RCA = right coronary artery; SVG = saphenous vein graft.

TABLE III Procedural Correlates of Ectasia After Directional Atherectomy

Features	Ectasia— No. (%)	No Ectasia— No. (%)	Likelihood Ratio	Univariate p Value
7Fr device	26 (53)	138 (45)	1.36	NS
DAR	0.76 ± 10	0.69 ± 11	—	<0.001
No. of specimens	7 ± 5	6 ± 5	—	NS
No. of passes	12 ± 7	11 ± 8	—	NS
Before PTCA	6 (12)	50 (15)	0.77	NS
After PTCA	2 (4)	38 (12)	0.33	NS
Postprocedural angiography				
Haziness	18 (38)	113 (39)	0.94	NS
Irregularity	8 (17)	51 (18)	0.94	NS
Dissection	17 (35)	66 (23)	1.87	0.057
Perforation	9 (0)	2 (1)	*	NS

*Not performed owing to no observation in the ectasia group.
DAR = device artery ratio; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

TABLE IV Early and Late Outcome After Directional Atherectomy

	Ectasia—No. (%)	No Ectasia—No. (%)	Likelihood Ratio	Univariate p Value
Clinical outcome				
Abrupt closure	2 (4)	23 (7)	0.55	NS
Myocardial Infarction	1 (2)	4 (1)	1.63	NS
Coronary bypass surgery	1 (2)	18 (5)	0.35	NS
Death	0 (0)	3 (1)	*	NS
Restenosis†	17 (61)	80 (50)	1.62	NS
Intimal hyperplasia (mm^2)	8.3 ± 8.9	2.4 ± 5.0	*	0.002

*Not performed due to no observations in the ectasia group.
†Analysis includes 188 patients with angiographic follow-up.
NS = not significant.

the atherosclerotic lesion,[5] although a significant degree of mechanical dilatation may also occur.[4] Compared with standard balloon angioplasty, less angiographic dissection has been reported with directional atherectomy.[18,19]

Despite these findings, the optimal depth of resection by directional atherectomy is not known. Larger luminal dimensions immediately after directional atherectomy have resulted in a lower incidence of late restenosis,[10] but deeper atheroma resection may be associated with retrieval of media and adventitia. In saphenous vein graft lesions, resection of normal vessel wall has been correlated with higher rates of restenosis.[9] Furthermore, vessel perforation may occur with more aggressive atheroma resection by directional atherectomy.[1]

Dilatation beyond the normal arterial lumen, defined angiographically as ectasia, is an uncommon finding after coronary angioplasty.[20–22] To date, the incidence and clinical implications of ectasia after directional atherectomy have not been reported. In the present series, ectasia occurred in 50 of 382 procedures (13%). Ectasia occurred more often in lesions within the circumflex coronary artery, presumably due to the more severe angulation of the circumflex artery, and less frequently in lesions within the right coronary artery. In general, qualitative morphologic findings were not correlated with ectasia, although it was more frequent in complex, probably thrombus-containing lesions. Normal arterial diameters were smaller and device:artery ratios were higher in lesions with postprocedural ectasia, suggesting that oversized devices contributed to the deeper tissue resection in lesions with postprocedural ectasia. The incidence of postprocedural ectasia did not vary significantly between the early$^{1-20}$ and later operator (>20) experience. Although coronary dissection was performed more often in patients with ectasia, the presence of angiographic ectasia was not associated with an increased incidence of periprocedural complications.

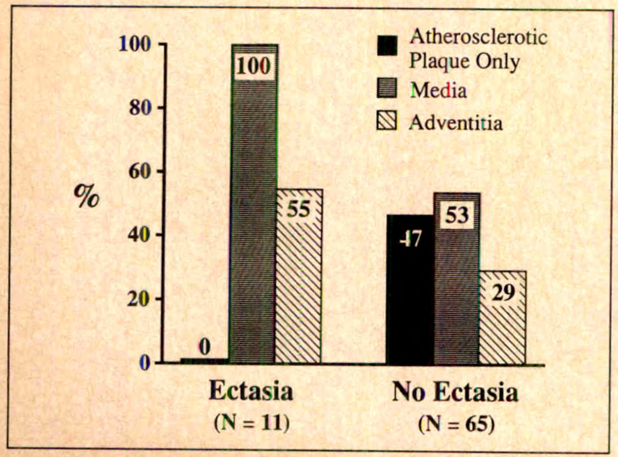

FIGURE 4. Histologic findings in lesions with angiographic ectasia after atherectomy. Adventitia or media, or both, were present in all patients with angiographic ectasia, but also present in 53% of lesions without angiographic ectasia.

In prior series, adventitia or media, or both, have been resected in 10 to 40% of lesions after directional atherectomy without apparent clinical sequelae.[4,8] In the present series, normal vessel wall was detected in all patients with angiographic ectasia, but was also present in 53% of lesions without ectasia. The present report also suggests an association between severe ectasia, defined by a residual area stenosis <−20%, and an increased incidence of restenosis compared with no ectasia (70 vs 50%; p = 0.12). Moreover, intimal hyperplasia, defined as the loss of luminal dimensions from the postprocedural to follow-up study, was significantly greater in lesions with postprocedural ectasia.

The present study has several important limitations. First, the proximal and distal normal segments were selected by virtue of their location relative to the stenosis and relatively smooth angiographic borders. In the present report, the definition of angiographic ectasia was based on selection of a normal reference segment. If the segment selected had significant luminal narrowing due to atherosclerosis not apparent angiographically, the frequency of excision into the normal vessel wall may have been overestimated. Second, major ischemic complications occur infrequently after directional atherectomy and the sample size in the present study may be insufficient to detect differences in patients with and without angiographic ectasia. Finally, the present study does not address whether resection of media and adventitia predisposes to subsequent intimal hyperplasia restenosis. The high rate of media and adventitia resection and restenosis in patients without angiographic ectasia suggests that further studies evaluating the effect of the depth of resection on restenosis are needed.

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Pulmonary Thallium-201 Uptake Following Dipyridamole-Exercise Combination Compared with Single Modality Stress Testing

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Angiographic and clinical determinants of pulmonary uptake of thallium-201 were assessed in a laboratory setting where supine bicycle exercise is used for stress testing in the absence of limiting pharmacologic or physical factors, and where symptom-limited exercise is added to intravenous dipyridamole infusion in other cases. Angiographic correlation was available in 400 patients, including 130 tested with exercise, 94 in whom only handgrip or abbreviated bicycle exercise could be used after dipyridamole, and 176 in whom intravenous dipyridamole was combined with a significant level of exercise. For each test mode, lung/myocardial ratios on the immediate image were highly correlated ($p \leq 0.001$) with a score based on the number of critical coronary artery stenoses, with grading by contrast ventriculography, and with the number of stenosed ($\geq 50\%$) arteries; relationships ($p < 0.05$) to history of myocardial infarction and to gender were also present. Multiple regression analysis showed the critical stenosis score and ventricular dysfunction to be the only significant determinants. When dipyridamole-based tests were compared with exercise, curves of receiver-operating characteristics showed a tendency to better diagnostic performance. When dipyridamole is incorporated in stress testing, the value of increased lung uptake as an ancillary diagnostic sign is similar to that established for exercise.

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In performing myocardial perfusion scintigraphy with thallium-201, an important objective is the identification of patients who have severe or multiple stenoses and consequently are at high risk for coronary events.[1] Previous studies[2–6] have evaluated indicators of high risk on myocardial scintigraphy performed with exercise stress. Increased pulmonary uptake of thallium-201[6–9] after exercise correlates with extensive coronary artery disease and with contraction abnormalities at rest; moreover, this scintigraphic finding appears to be a major determinant of prognosis for future cardiac events.[10,11] However, suboptimal levels of exercise or therapy with β blockers may increase lung uptake[7,8] and mask the extent of myocardial defects.[12]

The interpretation of ancillary findings on thallium-201 scintigraphy has been rendered more complex by the evolution of alternate stress test modalities. In patients who cannot exercise, pharmacologic coronary vasodilation with intravenous dipyridamole is an effective modality for scintigraphic assessment of myocardial ischemia.[13] Although a few studies have assessed the significance of pulmonary uptake of thallium-201 after dipyridamole stress,[14,15] the relationship of such ancillary scintigraphic signs to angiographic findings[16] and their predictive value is unsettled. The use of dipyridamole has drawbacks of (1) truncating the physiologic information available from exercise stress testing,[17] and (2) providing high abdominal background activity that may interfere with cardiac assessment.[18,19] The combination of intravenous dipyridamole and dynamic exercise testing has been assessed in a number of laboratories[18,19] and provides a method that is safe, scintigraphically preferable to dipyridamole alone, and capable of yielding ancillary physiologic information to accompany the scintigraphic data. Because the combined test mode exerts a more potent effect on coronary blood flow and on electrocardiographic and other indicators of ischemia than dipyridamole alone,[20] it might have a particular propensity to induce increased lung uptake of radiothallium.

In a previous study,[19] we identified patients referred for myocardial scintigraphy in whom it was suspected that interfering pharmacologic or noncardiac physical factors precluded performance of exercise to the end points of chest pain or appropriate tachycardia. In these patients, symptom-limited exercise was added to intravenous dipyridamole. With optimal patient selection, results of the combined stress mode could be compared with those obtained using exercise as the sole modality.

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In the present study, we investigated the role of angiographic and clinical determinants of lung uptake of thallium-201 in patients assigned to a stress modality using the described triage scheme.

METHODS

Patients: Patients in this study were chosen from a series of approximately 3,000 referrals for myocardial perfusion scintigraphy between June 1985 and March 1989. During this interval, patients were assigned to stress testing with a specified modality[19] according to the scheme described in Figure 1.

The 400 patients with angiographic correlation were selected according to the following criteria: (1) no history of angioplasty or coronary bypass surgery before scintigraphy, (2) correlating coronary arteriography and contrast ventriculography performed within 3 months of scintigraphy, and (3) neither test (scintigraphy or angiography) performed within 1 week after a myocardial infarction. Some additional patients were excluded for the following clinical and technical reasons (<10 for each criterion): (1) cardiac catheterization showing a major component of valvular heart disease, (2) clinical and angiographic findings suggesting nonischemic cardiomyopathy, (3) incorrect timing of immediate thallium-201 scintigraphic images, and (4) scintigraphic images not archived on magnetic tape.

Assignment of stress modality: Patients were evaluated on presentation at the Nuclear Medicine Department. The purpose of the selection system was to provide an optimal stress test for all patients, which would permit the detection of reversible myocardial perfusion defects. The assessment included a detailed interview with respect to current symptoms, exercise tolerance, drug therapy, and review of prior stress tests. These data were incorporated into an estimate of whether the patient could perform bicycle exercise to a suitable end point, i.e., reproduction of cardiac symptoms or attainment of an adequate exercise heart rate. Exercise alone was considered an appropriate test mode if effort characteristically induced the symptoms and if interfering drugs and physical factors were absent.

For the remaining patients, intravenous dipyridamole was selected, as potential exercise performance was suboptimal. The presence of intercurrent medical conditions, including peripheral vascular disease, musculoskeletal disorders or pulmonary disease, was established by interview for most of this group; other patients were taking drugs (e.g., β blockers or verapamil) that inhibit optimal heart rate response and could diminish the size of perfusion defects.[12] When patients could not undertake bicycle exercise, because of early onset of chest pain during dipyridamole infusion or because of severe physical limitations (e.g., hip osteoarthritis), they performed handgrip or ankle-flexion exercise, or both, for 2 to 4 minutes.[21] Dipyridamole-based tests were classified according to the level of exercise attained. Patients achieving ≥3 minutes of progressive bicycle ergometry were considered to have undertaken the combined test; those who performed only handgrip or abbreviated bicycle exercise after dipyridamole were considered to have undergone stress testing primarily with the drug.

The 3 test mode groups (exercise, dipyridamole and combination) were similar with respect to most clinical and angiographic characteristics including age, Q waves, ventricular dysfunction and coronary stenoses. However, the distribution of gender varied among the groups. Thus, men accounted for 87% of those tested with exercise, 45% of those tested with dipyridamole, and 80% of those tested with the combination.

Stress techniques: Monitoring of patients during stress testing was performed using manual sphygmomanometry and 12-lead electrocardiographic recordings. Pretest blood pressure recordings were obtained by careful technique.[22] Supine exercise stress testing was performed using a bicycle ergometer located on the imaging table.[19] Intravenous dipyridamole was infused ac-

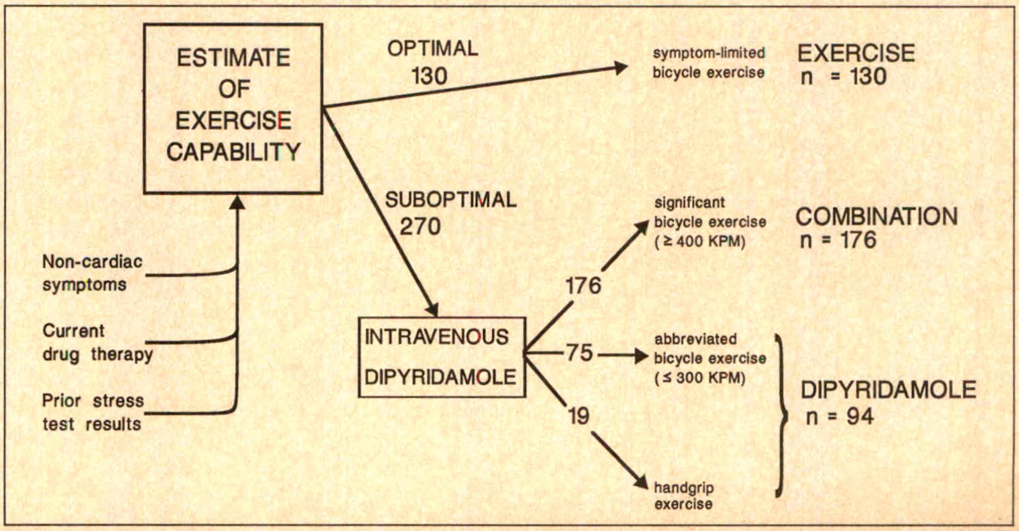
ESTIMATE OF EXERCISE CAPABILITY
OPTIMAL 130
symptom-limited bicycle exercise
EXERCISE n = 130
SUBOPTIMAL 270
Non-cardiac symptoms
Current drug therapy
Prior stress test results
INTRAVENOUS DIPYRIDAMOLE
176
significant bicycle exercise (≥ 400 KPM)
COMBINATION n = 176
75
abbreviated bicycle exercise (≤ 300 KPM)
19
handgrip exercise
DIPYRIDAMOLE n = 94

FIGURE 1. Scheme for assignment of referred patients to a stress/imaging modality in use since 1985. Patients were initially assessed to estimate their ability to exercise to an adequate end point (cardiac symptoms or target heart rate). When exercise ability was estimated to be suboptimal, intravenous dipyridamole was administered followed by exercise to tolerance. Of the 400 angiographically correlated patients in the study, 130 were tested with symptom-limited bicycle exercise alone. In 270, intravenous dipyridamole was administered followed by exercise.

cording to established protocols.[13-15] The addition of bicycle exercise to dipyridamole was performed as previously described.[19] First, 0.57 mg/kg of dipyridamole was infused over 4 minutes; immediately thereafter, bicycle exercise was begun with gradually increasing work loads every minute until limiting symptoms occurred.

Protocol for myocardial scintigraphy: A mobile gamma camera interfaced with a computer was used for imaging. A large antecubital vein was used where possible for injection. During peak stress, thallium-201 chloride was rapidly injected into a rapidly flowing saline intravenous access; exercise was continued for at least 1 minute after tracer injection. Immediate perfusion images were recorded at 4 minutes after peak exercise. The imaging sequence began with the 40° left anterior oblique view and was followed by anterior and 80° left anterior oblique projections. Redistribution images were obtained in the same projections at 2 to 4 hours after stress testing.

Quantitation of pulmonary uptake: After retrieval from magnetic tape, the immediate 40° left anterior oblique images were used for quantitation of lung uptake.[19,23] Uptake in a crescentic left lung region was compared with the peak myocardial segment uptake. The reliability of pulmonary uptake measurements was addressed in 40 patients. Images were randomly selected and stored on a computer disc. Sets of values calculated by 2 observers correlated with a coefficient of 0.97. In a group of 35 studies with low probability for coronary artery disease,[23] the upper limit of normal was 51%, with no difference among the test modes.

Cardiac angiography: Coronary artery stenoses were graded by a cardiovascular radiologist unaware of the results of perfusion imaging. Stenoses were regarded as significant if they resulted in luminal narrowing ≥50%, or critical if they resulted in luminal narrowing ≥90%; a stenosis of 70% in the left main stem was regarded as critical. In all, 66 patients had normal coronary arteries or insignificant lesions and were categorized as being normal. Patients with coronary artery disease were categorized according to the number of 50% stenoses, and also according to a critical disease score. The critical score was defined as follows: a score of 3 was assigned for a critical left main stem lesion; 2 for a critical proximal left anterior descending artery lesion; 1 for a critical lesion in the right, left circumflex, intermediate artery or distal left anterior descending artery; and 0.5 for a critical lesion in a branch artery. The total number of points was summed to establish a score for each patient.

Ventricular function was graded on a 5-point scale on biplane contrast ventriculography by a single observer. The grade was based on the number of hypokinetic segments, with additional weight given to the septum; a score of 1 implied normal function and 5, global hypokinesia.

Categorization of clinical variables: The presence of a myocardial infarction was categorized according to a 3-level scheme according to the history and the electrocardiogram at rest obtained at the time of evaluation in the Nuclear Medicine Department. In 194 patients, history and electrocardiographic evidence of myocardial infarction were absent. In 90 patients there was either a history of myocardial infarction or pathologic Q waves. In 116, a history of infarction and Q waves were both present. The presence of hypertension was also categorized according to a 3-level scheme, based on a prior history of high blood pressure readings, blood pressure measurement at the time of scintigraphy, and antihypertensive medication.[22]

Statistical analyses: Analysis of variance[24] was performed to determine the relation of lung uptake to test mode, and angiographic and clinical variables. Angiographic variables considered were the number of diseased coronary arteries, the critical stenosis score, and the rating by contrast ventriculography. Clinical variables considered were gender, hypertension and prior myocardial infarction. Follow-up comparisons were made using Scheffe's test.

Univariate correlations were obtained with each of the clinical and angiographic variables for each test mode. Multiple regression analyses[24] were then performed. The significantly contributing variables were established, and revised regression equations derived; confidence limits for the regression coefficients were then determined. Similarly, regression equations were derived separately for groups with 1-, 2-, and 3-vessel coronary artery disease (defined by the number of arteries with 50% stenoses).

Receiver-operating characteristic curves were analyzed[25] using 18 thresholds for quantitative lung uptake to separate normal from abnormal; this technique was applied against 2 angiographic criteria for disease. In the first, pulmonary uptake was determined as an indicator of coronary artery disease, i.e., any stenosis ≥50%. In the second, lung uptake was considered as a diagnostic indicator of severe coronary stenoses; a critical score ≥2 was used to indicate severe disease.

RESULTS

Relation of pulmonary uptake to angiographic findings: Lung uptake of thallium-201 increased progressively with the number of diseased coronary arteries (Figure 2). Analysis of variance showed that there was no significant difference among the test modes in the pattern. Still stronger relations were seen with the critical stenosis score, and with the grade of contrast ventriculography. Figure 3 shows the relation of lung uptake to the critical stenosis score, with patients having scores of 1.5 demonstrating higher levels than those with no critical stenoses ($p < 0.001$).

Correlation with clinical variables: Figure 4 shows the relation between lung uptake and evidence of prior myocardial infarction for each test mode. Those with a history of infarction and Q waves had higher levels than those in whom such a history was absent. Other clinical variables were less well related to lung uptake. In general, women had lower values than men, but this difference only reached significance for studies performed with dipyridamole alone or the combined test. No relation was seen between lung uptake and the presence or history of hypertension.

Multiple regression analysis: With the techniques of multiple regression, all 3 test modes were shown to depend in a similar fashion on the angiographic and clinical variables (Table I). For each test mode, there was a highly significant relation to the critical stenosis score, and a less significant relation to grade by contrast ventriculography. When critical stenosis score was included in the analysis, the number of stenosed arteries was not significant for any of the test modes (p ≥0.5). Similarly, patient gender, a history of myocardial infarction, and presence of hypertension were not significant contributors to lung uptake.

Table II lists the regression equations that characterize dependence of lung uptake on the 2 important angiographic determinants for each test mode. Although the regression weight for critical stenosis score was higher for combined exercise and dipyridamole than for the single modality tests, this difference did not reach statistical significance.

Furthermore, as shown in Table II, the relationship of lung uptake to these angiographic determinants was derived for each level of coronary artery disease (i.e., for 1- 2- and 3-vessel disease using the criteria of 50% stenosis); a dependence of lung uptake on the critical stenosis score was observed in each case (p ≤0.01).

Receiver-operating characteristic curves: When increased lung uptake was used as an indicator of severe disease, some differences were seen between the performance of the 3 test modes (Figure 5). Thus, the curves for dipyridamole and for the combined test were situated to the left of the curve for exercise. However, these curves did not differ statistically. Similar findings were seen when increased lung uptake of thallium-201 was assessed as a diagnostic criterion for any level of coronary artery disease. In this case, the curves for dipyridamole and for the combined test lay to the left of the

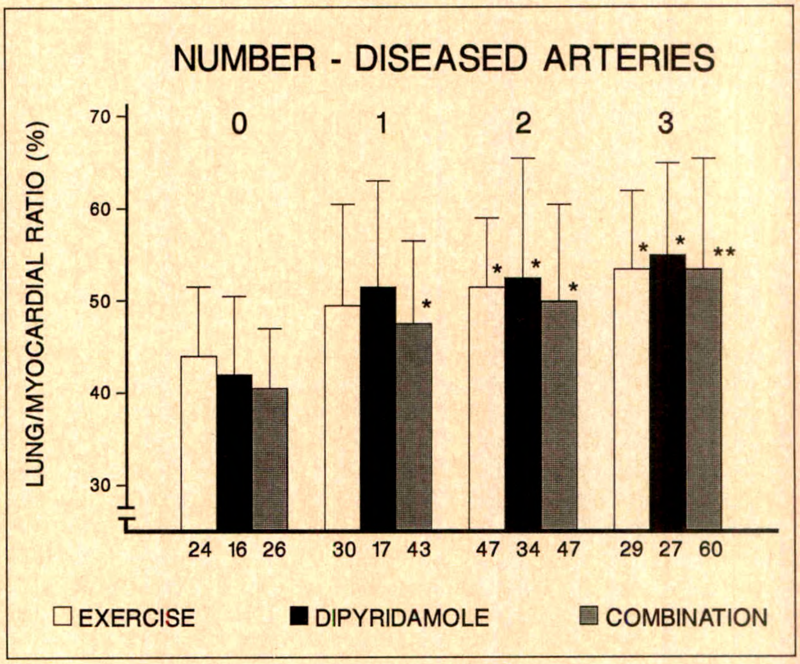

FIGURE 2. Pulmonary uptake of thallium-201 in relation to the number of diseased coronary arteries (50% stenosis is used as a criterion). The number of patients tested with each modality is shown *below the bars,* which give the mean (standard deviation) for the left lung/myocardial ratio. Analysis of variance showed a significant overall effect of the number of diseased arteries (p <0.0001), but no effect of test mode (p = 0.15). The more severely diseased groups show an increase compared with those with no significant stenoses. *p <0.05; **p <0.001.

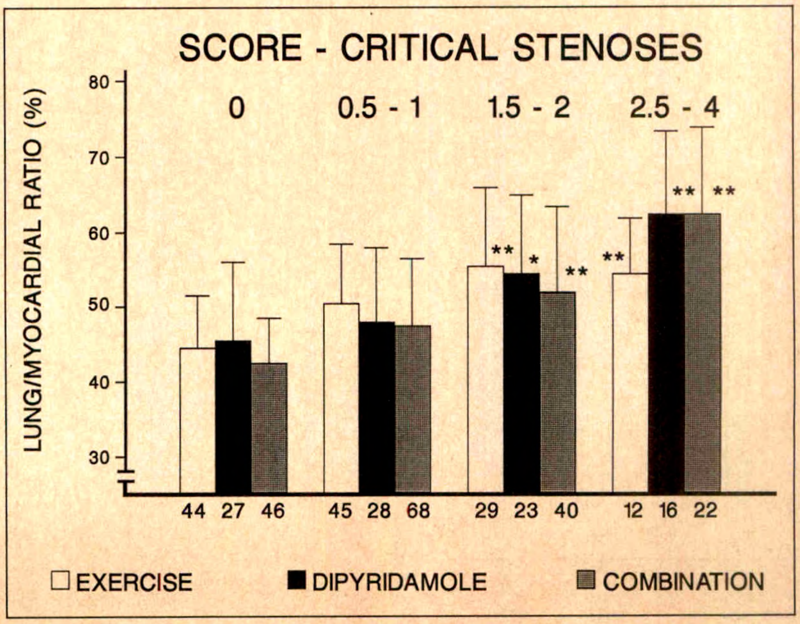

FIGURE 3. Pulmonary uptake of thallium-201 in relation to the critical stenosis score. Values for the score were grouped as shown. The number of patients tested with each modality is shown *below the bars,* which give the mean (standard deviation) for the left lung/myocardial ratio. Analysis of variance showed an overall effect of critical stenosis level (p <0.0001), but no effect of test mode (p = 0.5). Groups with higher scores for critical stenoses differ from those with no critical lesions. *p = 0.05; **p <0.001.

TABLE I Lung Uptake of Thallium-201: Multiple Regression Analysis

	Probability (p) Values—Test Mode		
Determinant	Exercise (n = 130)	Dipyridamole (n = 94)	Combination (n = 176)
Score (critical stenoses)	0.006	0.01	<0.0001
Grade (ventriculography)	0.03	0.03	0.01
Number (stenosed arteries)	0.5	0.9	0.8
Infarction	0.5	0.2	0.3
Gender	0.9	0.2	0.2
Hypertension	0.9	0.3	0.9

TABLE II Lung Uptake of Thallium-201: Regression Equations

	Pulmonary/Myocardial Ratios (%)			
		Regression Weights (95% confidence limits)		
Group	Intercept	Score (critical stenoses)	Grade (ventriculography)	Multiple Correlation (r)
Exercise (n = 130)	42	3 (1–5)	2 (1–4)	0.50
Dipyridamole (n = 94)	41	4 (1–7)	2 (0–4)	0.53
Combination (n = 176)	39	5 (4–7)	2 (0–3)	0.58
1-Vessel (n = 90)	44	5 (1–8)	NS	0.32
2-Vessel (n = 128)	39	4 (3–6)	3 (1–4)	0.49
3-Vessel (n = 116)	41	4 (2–6)	2 (1–3)	0.49

NS = not a significant determinant.

exercise curve over much of the useful portion of the curve (false-positive rate <50%).

DISCUSSION

In the present study, we found that increased lung uptake of thallium-201 after testing performed with a combination of intravenous dipyridamole and exercise, reflects severe and extensive coronary artery disease. With the combined test, or indeed with either single modality, a score based on the number and location of severe coronary artery stenoses was found to be the best determinant of increased pulmonary/myocardial ratios.

A considerable volume of published reports attests to the role of increased lung uptake of thallium-201 as an ancillary finding during exercise stress testing.[1,6-9] The presence of increased uptake correlates with angiographic variables, and generally indicates more severe coronary artery disease or left ventricular dysfunction. Previous studies have observed good specificities of pulmonary uptake for coronary artery disease, but incomplete sensitivity. A number of other reports[10,11] ascribe a major prognostic value to pulmonary uptake of thallium-201, although the difficulty in performing these studies must be recognized in settings in which scintigraphy contributes to the decision for intervention with surgery or angioplasty. Presumably, increased lung uptake in some patients with coronary lesions reflects the functional significance of the stenoses and therefore is of prognostic value.

The current study's method of measuring lung uptake differs somewhat to that quoted in previous reports. We measured pulmonary/myocardial ratios on the left anterior oblique image, whereas most other investigators have used an anterior image. Our specific protocol derives from our interest[23] in assessing ventricular function as well as pulmonary uptake on perfusion images synchronized to the electrocardiogram. (Left ventricular contractile function can be disclosed more readily on the left anterior oblique images.) Nonethe-

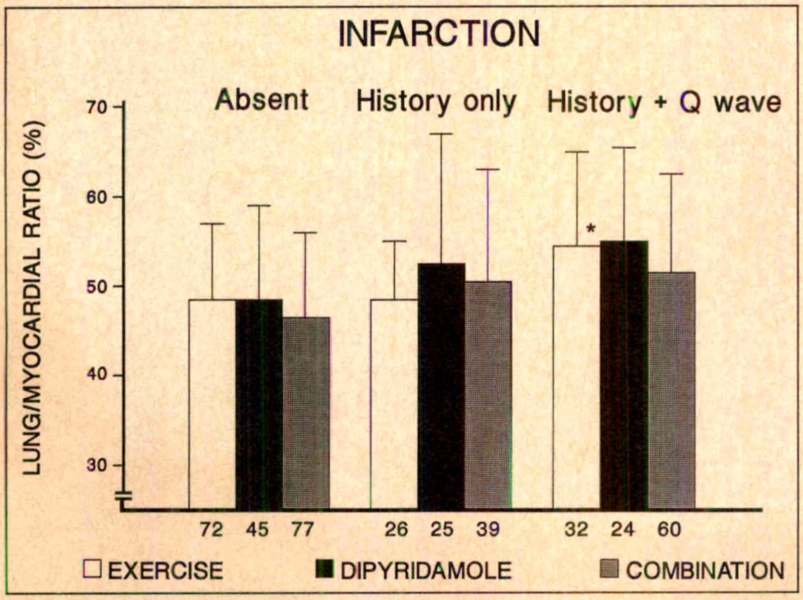

FIGURE 4. Pulmonary uptake of thallium-201 related to the presence of prior myocardial infarction. Patients were grouped according to history of infarction and the presence of Q waves. The number in each category tested with each test mode is shown *below the bars*, which give the mean (standard deviation). There was no overall significance of test mode (p = 0.2), although there was a significant relation to presence of infarction (p = 0.0002). The only group of patients that showed a statistically higher value was that tested by exercise with Q waves and a history of infarction. *p <0.05.

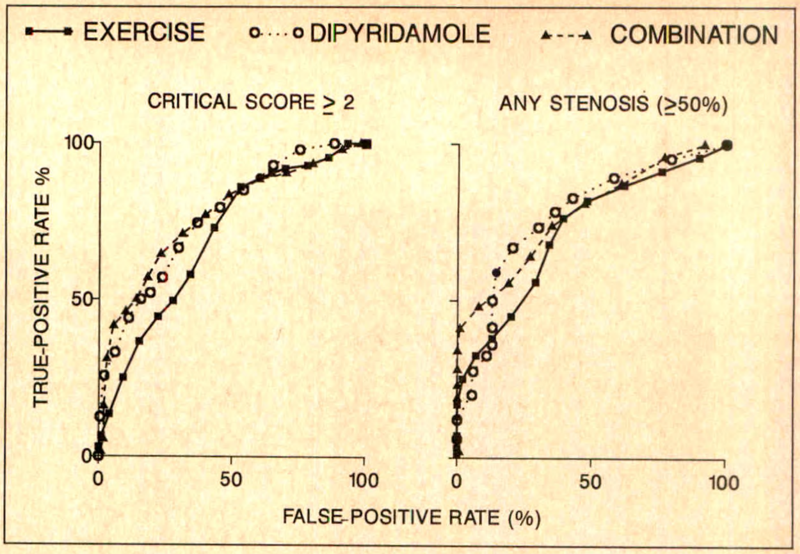

FIGURE 5. Receiver-operating characteristics for pulmonary thallium-201 uptake using 2 angiographically derived criteria. For each test mode, the true-positive rate is compared to the false-positive rate using varying levels of pulmonary uptake as a cutoff. In the *left-hand panel*, pulmonary uptake is considered as an index of severe disease (i.e., critical stenosis score ≥2.0). In the *right-hand panel*, pulmonary uptake is gauged as an index of coronary artery disease (i.e., any stenosis ≥50% is considered). Curves lying closer to the *upper left corner of the plot* reflect superior diagnostic performance.

less, we found similar relationships of lung uptake in this study to those in other studies of exercise stress which used different imaging projections and different quantitative algorithms.

Although other investigators[14,15] have addressed the significance of pulmonary thallium-201 uptake after intravenous dipyridamole infusion, previous studies have not evaluated the combination of intravenous dipyridamole and symptom-limited exercise or directly compared the various test modalities. The current study, in which supine exercise was used either alone or in conjunction with dipyridamole, evaluates different stress-testing methods in the same physiologic position. Moreover, our protocol for assignment of patients to stress-testing procedures allows comparison of the dipyridamole-based studies with exercise under optimal conditions. Suboptimal exercise stress may result in higher levels of pulmonary uptake of thallium-201[7] as well as decreased sensitivity in reflecting regional myocardial hypoperfusion.[26] In our laboratory, only patients who are estimated to be able to exercise to target heart rate or to the end point of chest pain (<50% of all who present for scintigraphy), are stressed with exercise alone. The potential advantage of the frequent use of dipyridamole in stress testing as in the current series has been discussed previously.[18,19]

Recent studies of the combination of dipyridamole and exercise suggest that it may have the potential to fully disclose the scintigraphic and functional consequences of coronary stenotic lesions.[18-20,27] To the extent that increased pulmonary uptake of thallium-201 is a functional consequence of stress in patients with critical stenoses, the combined stress procedure might bring out this abnormal finding more often than would single modality test modes. In the current study we did find that the receiver-operating characteristic curve for pulmonary uptake with dipyridamole-based tests was situated slightly to the left of the exercise curve; additionally, the regression coefficient for the combined test was higher than for either single modality test. However, the differences among the test modes did not reach statistical significance; the inherent technical and clinical variability in pulmonary uptake measurements may preclude a definitive comparison unless a crossover trial is undertaken.

Although pulmonary uptake of thallium-201 may have a prognostic value that exceeds its relation to definable angiographic variables, noninvasive testing in the clinical setting would be enhanced by development of ancillary markers that are more predictive of results of coronary arteriography.[28] Other reports[5,16] have suggested that left ventricular dilatation induced by stress would provide such an index, surpassing the sensitivity of abnormal pulmonary uptake. In our hands (unpublished results), indexes of stress-induced dilatation have proved disappointing in this regard. However, we have shown that qualitative and quantitative data on left ventricular contractile function can be derived from perfusion images synchronized to the electrocardiogram, and that immediate post-stress images may reflect stress-induced dyskinesia.[23] Further studies comparing these indexes with respect to angiographic correlations and prognostic use will be of value.

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Survey of Practicing Cardiologists in Maryland on Their Choice of Thrombolytic Therapy for Acute Myocardial Infarction

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In November 1990, we surveyed 160 practicing community cardiologists in the state of Maryland and 20 academic cardiologists at the University of Maryland Medical Center to determine each individual's preference for aggressive versus nonaggressive therapy for various presentations of acute myocardial infarction. The survey was repeated in April 1991 following a report of the results of the Third International Study of Infarct Survival. All 100 responding cardiologists chose aggressive therapy to manage an early (<2 hours) acute anterior myocardial infarction in a 50-year-old patient. However, less aggressive therapy was chosen by many community cardiologists for management of early inferior acute myocardial infarction or for elderly patients. Most community cardiologists chose tissue plasminogen activator as their thrombolytic drug of choice, whereas university cardiologists favored streptokinase. Although there were substantial shifts in choice of thrombolytic agent on the repeat survey, most community physicians still chose tissue plasminogen activator over the less expensive streptokinase.

(Am J Cardiol 1992;69:327–330)

Recent reviews have examined current recommendations regarding selection criteria of patients with acute myocardial infarction (AMI) for thrombolytic therapy and have contrasted various thrombolytic agents.[1–3] Controversy exists as to which, if any, of the commercially available thrombolytic agents is best used in each specific clinical circumstance associated with AMI. The role of primary angioplasty also remains controversial.[4–6] Two recent large randomized studies have suggested no obvious mortality benefit in patients randomized to the more expensive thrombolytic agent tissue plasminogen activator over the less expensive agent streptokinase.[7–9]

To determine current perceptions of cardiologists in the state of Maryland, a mail survey was conducted in November 1990 and repeated in late April 1991, following widespread media announcement of the results of the Third International Study of Infarct Survival.[9–12]

METHODS

Questionnaires were initially sent to 160 practicing cardiologists registered with the Maryland Medical and Chirurgical Society and 20 cardiologists and fellows at the University of Maryland Hospital. The questionnaires addressed 6 clinical vignettes and gave the clinician choices between intravenous thrombolytic agents (streptokinase, tissue plasminogen activator, anisoylated plasminogen streptokinase activator complex [APSAC], or urokinase), primary percutaneous transluminal coronary angioplasty, or none of the preceding choices. In addition, the practitioner was asked if his or her choice would be different (1) if a catheterization laboratory were immediately available, (2) if the patient were a member of the physician's family, or (3) if there were no differences in cost. Questionnaires were returned by 82 community cardiologists (51%) and 16 university cardiologists (80%). Repeat questionnaires were returned by 45 of 82 community cardiologists who had initially responded and by all 16 university cardiologists. "Aggressive therapy" was defined as either intravenous thrombolytic therapy or primary percutaneous transluminal coronary angioplasty. Comparison between choices for patient groups or between community and university physicians were performed using the chi-square statistic with Yates correction for continuity or Fisher's exact test. A p value <0.05 was considered significant.

RESULTS

Initial survey in November 1990: Results are tabulated in Tables I and II. Therapeutic decisions were sig-

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TABLE I Choices of Community Cardiologists in the State of Maryland (n = 82)

Pt. No.	Pt. Age (years)	Site of Infarction	Time from Onset (hours)	SK	TPA	APSAC	PTCA	Other/ Nothing
1	50	Anterior	<2	12	65	5	0	0
2	50	Inferior	<2	14	47	4	0	17
3	50	Anterior	5	7	64	6	1	2
4	50	Inferior	5	6	32	5	0	39
5	80	Anterior	<2	10	56	3	1	12
6	80	Inferior	5	4	18	2	0	58

APSAC = anisoylated plasminogen streptokinase activator complex; PTCA = percutaneous transluminal coronary angioplasty; SK = streptokinase; TPA = tissue plasminogen activator.

TABLE II Choices of Cardiology Faculty and Fellows at University of Maryland Medical Center (n = 16)

Pt. No.	Pt. Age (years)	Site of Infarction	Time from Onset (hours)	SK	TPA	APSAC	PTCA	Other/ Nothing
1	50	Anterior	<2	10	4	1	1	0
2	50	Inferior	<2	12	3	1	0	0
3	50	Anterior	5	4	11	0	1	0
4	50	Inferior	5	5	4	0	0	7
5	80	Anterior	<2	8	4	1	2	1
6	80	Inferior	5	4	1	0	0	11

Abbreviations as in Table I.

nificantly influenced by location and time of the myocardial infarction, and age of the patient. Choices differed between community and university cardiologists. All cardiologists chose aggressive therapy for early (<2 hour) anterior AMI in a 50-year-old patient (patient 1). However, for inferior AMI in similar circumstances (patient 2), aggressive therapy was withheld by 17 community cardiologists (21%) but no university cardiologist. The choice of aggressive therapy for early anterior versus early inferior AMI was significantly different for community cardiologists ($p < 0.05$) but not for university cardiologists. For later (5 hour) anterior AMI in a 50-year-old patient (patient 3), only 2 community and no university cardiologists withheld aggressive therapy. Whereas therapeutic choices were similar for early and late anterior infarction in a 50-year-old, both cohorts were more likely to be nonaggressive for later inferior AMI (patient 4) than for early inferior AMI (patient 2) ($p < 0.05$). For an 80-year-old with anterior AMI within 2 hours (patient 5), 12 community cardiologists (15%) withheld aggressive therapy compared with only 1 university cardiologist ($p < 0.05$). Unlike community cardiologists, university cardiologists appeared as aggressive in treating an 80-year-old as a 50-year-old with early anterior AMI. However, when choosing therapy for an 80-year-old with inferior AMI at 5 hours, the majority of both groups chose less aggressive therapy. The difference between community and university cardiologists in treating an 80-year-old was different for early anterior AMI ($p < 0.05$), but not for late inferior AMI (p = not significant).

Interestingly, the choice of specific thrombolytic drug varied significantly between community and university cardiologists, particularly for treatment of early AMI. The majority of community physicians chose tissue plasminogen activator as their preferred thrombolytic agent, whereas the majority of university cardiologists chose streptokinase ($p < 0.05$). Community cardiologists chose tissue plasminogen activator as their thrombolytic agent of choice for all clinical scenarios, whereas university cardiologists switched to tissue plasminogen activator as majority choice only for late anterior AMIs in a 50-year-old (patient 3) ($p < 0.05$). APSAC and primary angioplasty were preferred by only a small minority of either group.

Additional questions: Of the 17 community cardiologists choosing streptokinase or APSAC as their drug of choice, 12 replied that their choice might have been different if cost were not a consideration, whereas 6 of 11 university cardiologists responded similarly. Availability of an immediate catheterization laboratory "might" have influenced therapy in 33 community and university cardiologists. Two community cardiologists replied they would have preferred members of their family be taken to the catheterization laboratory.

Repeat survey in 1991: Results for the 45 community and 18 university cardiologists who returned both surveys are listed in Table III. For every clinical vignette except patient 6, the number of cardiologists choosing streptokinase increased. There were significant increases in the choice of streptokinase as treatment for both patients 1 and 3 for community and university cardiologists. Community cardiologists significantly increased the choice of streptokinase for patient 5 and tended to do similarly for patients 2 and 4 (both $p < 0.08$). The vast majority of community and university

TABLE III Comparison of Choices Between Two Surveys—November 1990 Versus April 1991

Pt. No.	SK 90 (91)	TPA 90 (91)	APSAC 90 (91)	PTCA 90 (91)	Other/Nothing 90 (91)
Community Cardiologists (n = 45)					
1	9 (19)*	34 (25)	2 (1)	0 (0)	0 (0)
2	11 (19)†	22 (19)	1 (1)	0 (0)	11 (6)
3	3 (13)*	38 (30)	2 (1)	0 (0)	2 (1)
4	4 (10)†	20 (14)	1 (1)	0 (0)	20 (20)
5	9 (18)*	27 (20)	2 (2)	1 (1)	6 (4)
6	3 (3)	3 (6)	0 (1)	0 (0)	39 (35)
University of Maryland Medical Center Cardiologists (n = 16)					
1	10 (15)*	4 (1)	1 (0)	1 (0)	0 (0)
2	12 (15)	3 (1)	1 (0)	0 (0)	0 (0)
3	4 (12)*	11 (4)	0 (0)	1 (0)	0 (0)
4	5 (8)	4 (1)	0 (0)	0 (1)	7 (6)
5	8 (11)	4 (3)	1 (0)	2 (1)	1 (1)
6	4 (4)	1 (0)	0 (0)	0 (0)	11(12)

*$p < 0.05$; †$p < 0.08$ for streptokinase in 1991 versus 1990.
Abbreviations as in Table I.

cardiologists continued nonaggressive therapy for patient 6.

DISCUSSION

Over the last decade, numerous large prospective randomized national and international trials have evaluated the benefit of intravenous thrombolytic therapy for patients after AMIs.[13-17] Current controversies include patient eligibility criteria and thrombolytic drug selection.[1-3] Whereas there appears to be universal agreement in the decision to treat younger patients with an anterior AMI seen early after onset of symptoms, therapy in other clinical scenarios is less clear.

Community cardiologists appear less aggressive in treating all patients with inferior AMI and in treating older patients in general. Despite this, the majority did choose thrombolytic therapy for early inferior AMI in a 50-year-old and for early anterior AMI in an 80-year-old. Despite initial data suggesting a lack of benefit for thrombolytic therapy in patients with inferior AMI,[13,18] more recent studies have demonstrated a benefit in treating inferior AMI, particularly when seen early after the event.[15,19,20] A surprisingly large percentage of community cardiologists omitted thrombolytic drugs for inferior AMI, even when seen early. Few studies have addressed thrombolytic therapy in older patients, but recent evidence suggests the older patient may have the most to benefit from thrombolytic therapy.[1,15-17] University of Maryland cardiologists appear more aggressive in using thrombolytics for all patient examples given here, except for late inferior AMI in an older patient.

The difference of choice of thrombolytic agent between university and community cardiologists is intriguing. Several studies have demonstrated higher early patency rates with tissue plasminogen activator compared with other thrombolytic drugs.[21-23] More recent head-to-head comparisons between the drugs have not demonstrated an advantage in late patency, effect on left ventricular function, or mortality among these drugs.[7-9] Cost consciousness or peer pressure may have affected the thrombolytic agent choice of university cardiologists.[24]

Initial results of the International Study of Infarct Survival-3 were presented in March 1991 and suggested no substantial difference in mortality rates among patients randomized to the 3 thrombolytic agents.[9-12] Although this study has yet to be published in a peer-reviewed journal, the media has repeatedly suggested that physicians should switch to the less expensive agent streptokinase. The applicability of this study to United States practice continues to be debated.[25] Despite the on-going controversy, it is of interest that choices of therapy among cardiologists appear to be changing.

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Survey of Cardiac Pacing in the United States in 1989

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A survey of physicians who implant permanent cardiac pacemakers was conducted to identify practice patterns related to pacemaker-implantation frequency, hospital and implantation-facility characteristics, indications for pacing and pulse-generator replacement, preferences regarding device types, pacing modes, follow-up methods and frequency, and type and frequency of pacing-related complications. Questionnaires were sent to 11,414 potential physician respondents and 6 pacemaker manufacturers. Implanters' opinions were solicited regarding such issues as the importance of various device features and capabilities, the appropriateness of practice guidelines, and the efficacy of quality-assurance measures. In 1989, 89,445 primary pacemaker implantations and 21,055 pulse-generator replacements were performed by approximately 7,919 physicians at about 3,400 U.S. centers. Typically, a pacemaker manufacturer's sales representative played an active role in 80% of cases. Since the last survey, which examined pacing practices in 1985, primary implantations of dual-chamber pacemakers increased from 22 to 32%, and the proportion of adaptive-rate pacemakers increased from 1 to 40% of primary implants. The "typical" implanter used bipolar electrode systems in 90% of cases, single-chamber pacemakers in 70%, and the introducer method in 95% of lead placements. Significant differences in practice patterns were found among subsets of the survey respondents. Surgeons tended to work alone, use simpler, single-chamber pacemakers, and leave follow-up to others. Electrode stability tended to be better among implanters in nonacademic environments. The quadrennial survey continues to provide useful information on an easily identifiable and traceable patient population, but the process would be greatly simplified by the adoption of a "universal" reporting system such as that used in Europe.

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Surveys of practice patterns in cardiac pacing in the United States have been conducted periodically since 1969 and presented at the quadrennial World Symposium of Cardiac Pacing. The 1989 U.S. Survey is the seventh in a series that has identified changes in practice resulting from evolving technology, improved understanding of cardiac-conduction disorders, cost-containment concerns and regulatory issues. In recent years, the increasing availability of adaptive-rate pulse generators has created a new resource for chronotropically incompetent patients. The combination of rate modulation with dual-chamber pacing has resulted in clinical advantages for patients with a wide spectrum of rhythm disorders. The development of implantable defibrillators that incorporate antibradycardia (and even, in some cases, antitachycardia) pacing has changed existing treatment patterns for patients with life-threatening ventricular tachyarrhythmias.

The U.S. Survey has attempted to identify practice patterns related to pacemaker-implantation frequency, hospital and implantation-facility characteristics, indications for pacing and pulse-generator replacement, implantation techniques, device-type preferences, pacing modes, follow-up methods and frequency, and the frequency and character of pacing-related complications. Implanters' opinions were solicited regarding issues such as the importance of various device features and capabilities, the role of the pacemaker manufacturer's sales representative, the appropriateness of practice guidelines, and the efficacy of quality-assurance measures.

METHODS

Sources of data: Because there exists no complete list of physicians who implant permanent pacemakers in the U.S., a database of potential respondents was compiled from mailing lists supplied by several major pacemaker manufacturers and the North American Society of Pacing and Electrophysiology. After editing the composite database to minimize duplications and eliminate nonimplanters where possible, questionnaires were mailed to 11,414 potential respondents assumed to include all of the 7,919 implanting physicians in the U.S., an estimate derived from the results of a separate, concurrent survey of pacemaker manufacturers.

The 75-question implanters' questionnaire solicited information concerning type and volume of practice, indications for pacing, operative techniques, pacing modes, pacemaker programming and follow-up, complications encountered, and opinions regarding various pacing-related issues. The post office returned 334 questionnaires as undeliverable. Usable responses were received from 571 physicians, not counting those returned

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by nonimplanters and those otherwise unsuitable for inclusion in the analysis, yielding a sample that consisted of 7% of the country's 7,919 implanters. Of the numerical data received, approximately 38% were actual values and the remainder were estimates.

The 14-question manufacturers' questionnaire solicited information regarding pacemaker-implantation centers, implanters, device sales, implantation rates of primary and replacement pacemakers of various types, disposition of explanted pulse generators, warranty applicability, effects of regulations imposed by the U.S. Food and Drug Administration, and priorities for future development. It was distributed to 6 U.S. pacemaker companies (Cardiac Control Systems, Inc., Cardiac Pacemakers, Inc., Cook Pacemaker Company, Inc., Medtronic, Inc., Pacesetter Systems, Inc., and Telectronics/Cordis Pacemakers, Inc.), all of whom responded with the data requested, providing information gleaned in part from their own market research.

Data analysis: Data received from the implanters and manufacturers were encoded and entered in computerized databases for subsequent processing and statistical analysis, using dBXL and Quicksilver (Wordtech Systems, Inc.) for data processing and Absurv (Anderson-Bell, Inc.) for statistical calculations. The statistical analysis consisted primarily of calculating means, medians, marginal percents, and percents for various subsets of implanting physicians (e.g., surgeons and nonsurgeons). Median values were calculated to represent typical practices or opinions where means were thought to be inappropriate; chi-square or Fisher's tests of association, linear regression, and 1- and 2-tailed *t* tests were performed to identify statistically significant differences in practice patterns, therapeutic results, and opinions among subsets of implanters. Statistical significance was assumed when the null hypothesis could be rejected at the 0.05% level; except as indicated, all comparisons reported herein satisfied that criterion.

The respondents were divided for purposes of comparison according to medical specialty (surgeon or nonsurgeon), type of principal hospital (academic or nonacademic), and implantation volume (using a cutoff rate of 12 primary implantations per year to distinguish "high-volume" from "low-volume" implanters).[1] (For the purposes of the survey, an academic center was defined as a medical school or a hospital affiliated with a medical school.)

RESULTS

Demographics: From their market research, industry sources estimated that 89,445 primary implantations and 21,055 pulse-generator replacements were performed during 1989 by 7,919 implanting physicians at 3,400 U.S. centers, a total of 117,000 implantation procedures. The trend in pacemaker-implantation rate since 1969 is summarized in Figure 1, and a time profile of the breakdown of all permanent pacemaker implantations into primary pacemakers and pulse-generator replacements is shown in Figure 2.

From the median calculations it is possible to characterize the "typical" pacemaker implanter as a 44-year-old man who began implanting permanent pacemakers in 1979 and now works primarily in a single hospital, performing permanent pacemaker implantations in an operating room equipped with a fluoroscope. In 1989 he implanted 18 primary pacemakers, half for sick-sinus syndrome, and 35% for atrioventricular block, using the introducer technique in 95% of lead placements. Three quarters of his patients who underwent primary implantations were between 61 and 80 years of age. Of all the pacing systems he implanted, 90% were bipolar, 70% were single-chamber pacemakers, and 33% were adaptive-rate pacemakers. A pacemaker manufacturer's sales representative provided active assistance in 80% of his implantation procedures. (All percentages given in this report were rounded off to integer values except where greater precision was considered important.)

Roughly half of the respondents were surgeons; 97% were men. As a group, the surgeons were older than the nonsurgeons (mean age 49 vs 42). Surgeons and high-volume implanters tended to work in more hospitals than did nonsurgeons and low-volume implanters, working in 2 hospitals on the average. Whereas more than half of the respondents implanted pacemakers primarily at a single center, 1% worked in as many as 10 centers. Approximately 1% of respondents (primarily low-volume implanters) used outpatient "surgi-centers."

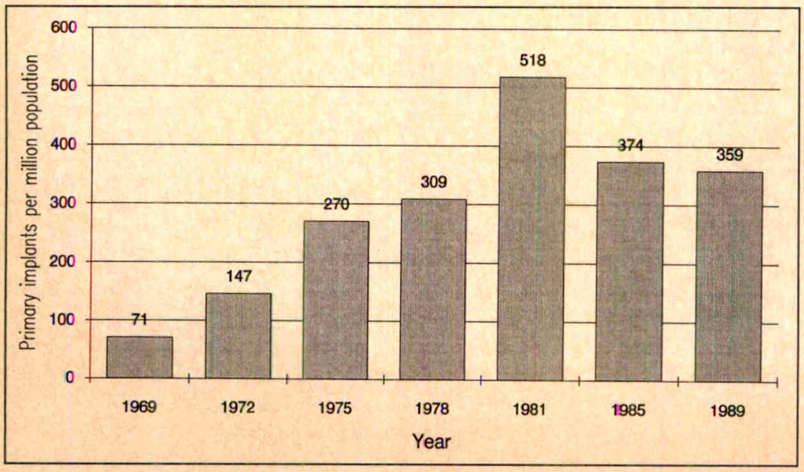

FIGURE 1. Trend in primary-pacemaker implantation rate over 20-year period showing increase of approximately 19 implantations per million population each year, not counting discontinuity in 1981. Manufacturing community sources estimate that figure for 1990 is 364 per million population.

Surgeons began implanting pacemakers earlier (mean year 1973) than did nonsurgeons (mean year 1980). Only 19% of respondents implanted cardiac defibrillators during 1989; these were primarily high-volume pacemaker implanters and those who worked mainly at academic centers. They implanted 1 to 54 such devices during the year (typically 6).

Primary center size ranged from 34 to 1,600 beds; the median bed size was 300. High-volume implanters worked primarily in larger institutions (median size 330 beds) than did low-volume implanters (median size 250 beds). Seventy-eight percent of respondents were affiliated with private or community hospitals, 17% with medical schools or affiliated institutions, and 3% with Veterans Administration and other hospitals. Fifteen percent worked in hospitals where there were special divisions or sections for clinical pacing, but this was less typical of surgeons, low-volume implanters, and those in nonacademic institutions. Written guidelines governing privileges for permanent pacemaker implantation existed in the principal hospitals of 66% of the respondents. Facilities for advanced electrophysiologic studies and special cardiac-electrophysiology divisions existed in the principal hospitals of 60% (vs 19%) of those affiliated with academic institutions, and in 32% (vs 14%) of the principal hospitals of high-volume implanters. Surgery for ventricular tachycardia was performed in the principal hospitals of 22% of the respondents, particularly those of high-volume implanters (27 vs 11%) and implanters affiliated with academic institutions (54 vs 15%).

Indications for pacing: Forty-eight percent of the primary pacemakers were implanted for sinus node dysfunction, a proportion that showed a decrease for the first time since 1975 (Figure 3). Atrioventricular node and His-Purkinje conduction disorders accounted for 45%, drug-induced bradycardia for 4%, and supraventricular and ventricular tachycardia for 2%. The sick-sinus syndrome was cited as an indication for pacing significantly more often by high-volume implanters (50 vs 44%). With this exception, no noteworthy differences in indications were found among the subgroups of implanters although significant differences in therapy, as reflected in the choice of pacing mode, were identified.

Eighty-seven percent of pulse-generator replacements were performed because of impending battery failure detected during follow-up; 6% were elective replacements prompted by indications such as anxiety, travel, device recall or advisory, infection, erosion, or the need for a change of pacing mode, and 5% were required because of actual, unanticipated pulse-generator failure.

Implantation practices: In general, implanters tended to work alone, although there were important differences. Nonsurgeons were more inclined than surgeons to work as part of a team in primary implantations (35

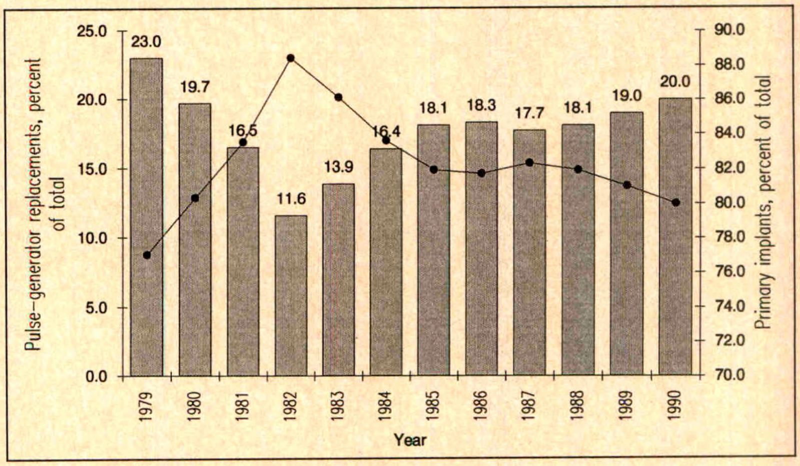

FIGURE 2. Time profile showing breakdown of permanent-pacemaker implantations into primary pacemakers *(line)* and pulse-generator replacements *(bars)* based on data obtained from surveys of pacemaker manufacturers.

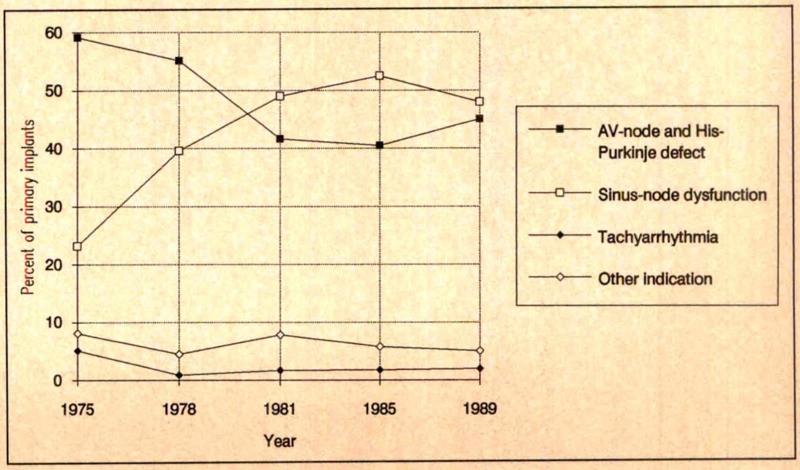

FIGURE 3. Trend in distribution of indications for primary pacemaker implantation since 1975. AV = atrioventricular.

vs 19%). Teamwork was much more common in primary implantations than in pulse-generator replacements (15 vs 3%). Implanters working in academic institutions tended to have higher primary implantation rates (31 vs 23/year).

Permanent pacemaker procedures were performed mainly in an operating room equipped with a fluoroscope (66%); 23% were performed in the cardiac catheterization laboratory, 5% in a special procedures room, and 4% in the x-ray department. Specialists tended to work in what they considered "their own" facility, with the operating room used far more frequently by surgeons (83 vs 47% of cases) and the catheterization laboratory by nonsurgeons (36 vs 10%).

Pacemaker manufacturers' sales representatives played an active role in most implantation procedures (mean 60%, median 80%), performing tests, making measurements, or operating equipment. Forty-one percent of the respondents used a sales representative in *all* of their procedures, whereas 39% *never* used their services in this way. According to a ranking by the respondents, sales representatives were helpful (in descending order of importance) in making measurements during implantation procedures, providing technical advice outside of the operating room, performing pacemaker programming, and conducting in-house training programs for clinicians. Surgeons tended to rely much more heavily on sales representatives for pacemaker programming, making measurements, and technical advice than did nonsurgeons.

Lead introducers were used in an average of 72% of each respondent's procedures, particularly by nonsurgeons (82 vs 62%), low-volume implanters (77 vs 70%), those associated primarily with nonacademic institutions (74 vs 66%), and those with fewer years of experience in pacing. Early electrode problems with active fixation unipolar leads in the ventricle occurred significantly more often when the introducer was used, especially by implanters who used the introducer method in >80% of cases. Use of the introducer was not correlated significantly with late electrode complications.

Active-fixation leads, such as corkscrew types, were used most frequently in the atrium (62% of cases). Passive-fixation leads equipped with tines or fins were used more often in the ventricle (85% of cases). Surgeons and nonsurgeons did not differ significantly in this respect. In all, active-fixation electrodes were used in an average of 66% of cases (especially by high-volume implanters), and passive-fixation electrodes were used in 34% (especially by low-volume implanters and those with more years of experience in pacing). Almost no respondents used electrodes with no fixation mechanism, and a transpericardial approach was used in only 2% of cases.

All implanters tended to prefer bipolar electrode systems in both the atrium and the ventricle; this was particularly true of nonsurgeons, who used bipolar atrial leads in 73% (vs 55%) of cases and bipolar ventricular leads in 76% (vs 60%). More experienced implanters (usually surgeons) used a significantly higher proportion of unipolar leads in both chambers.

Although an average of 95% of the respondents' primary implantations required hospital admission, approximately 43% of pulse-generator replacements were performed as outpatient procedures. The typical postoperative hospital stay was 2 days for primary pacemaker implantation and 1 day for pulse-generator replacement.

Pacing modes: Conventional single-chamber pacemakers (without rate modulation) were used in 36% of primary implantations; adaptive-rate single-chamber pacemakers were used in 32%. Conventional dual-chamber pacemakers were used in 24% of primary implantations; adaptive-rate dual-chamber pacemakers (some still undergoing clinical evaluation and therefore unavailable to most implanters) were used in 8%. The proportion of dual-chamber pacemakers used in primary implantations from 1975 through 1989 is shown in Figure 4.

The pacing modes (as designated by the NASPE/BPEG Generic Pacemaker Code)[2] most frequently chosen during 1989 were VVI (42%), VVIR (20%), DDD (14%), DDI (9%), and DDDR (9%). (These figures are weighted for each respondent's implantation volume and thus describe the use of each mode in the aggregate of pacemakers implanted by the respondents taken as a group.)

Electrode and pulse-generator problems: Early electrode problems (within 2 weeks of implantation) such as dislodgment and perforation were encountered seldom, but in the ventricle were more common with

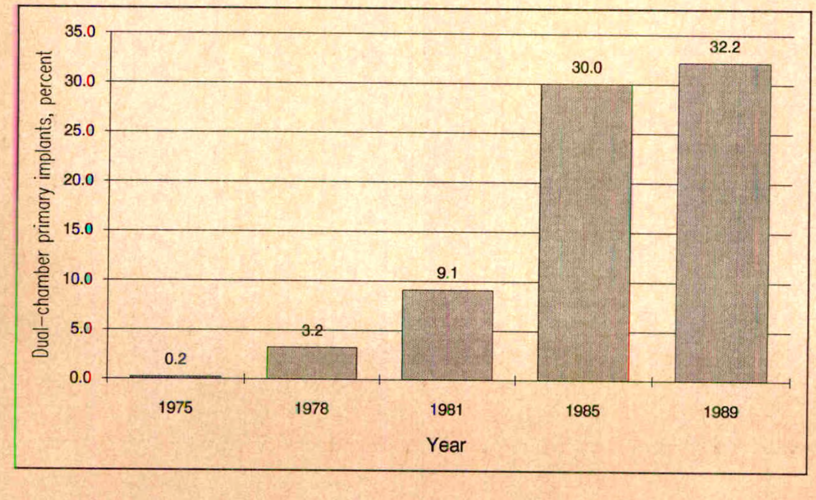

FIGURE 4. Trend in use of dual-chamber modes for primary pacemakers since 1975. Several models of DDD pacemakers first became commercially available between 1981 and 1985.

passive- than with active-fixation electrodes (1.4 vs 0.5% for unipolar electrodes, 3 vs 1% for bipolar electrodes). Late electrode problems (after 2 weeks) also were uncommon, but in the ventricle occurred more frequently with passive-fixation electrodes (1.3 vs 0.3% for unipolar electrodes, 1.3 vs 0.7% for bipolar electrodes). Atrial electrode complications occurred most frequently during the first 2 weeks, approximately twice as often with bipolar electrodes and 4 times as often with unipolar electrodes. The principal indication for pulse-generator replacement was normal battery depletion (87% of replacements; the typical figure, as indicated by the median, was 95%). The indications for elective and emergency pulse-generator replacement are summarized in Figures 5 and 6, respectively. Lead replacement was prompted primarily by high stimulation threshold, insulation failure, electrode displacement, and conductor fracture (Figure 7).

Pacemaker programming: An average of 42% of primary pacemakers were programmed before they were implanted (typically 30%). Of those not reprogrammed until *after* implantation, 33% were programmed within 5 days and 35% from 5 days to 3 months; 33% were not programmed within 3 months of implantation, particularly those implanted by solo implanters. Thus, 19% of all pulse generators implanted were left as programmed by the manufacturer.

Pacemaker follow-up: A pacemaker follow-up clinic existed in 43% of the respondents' primary institutions. For the purposes of the survey, a clinic was defined as a service performing evaluation procedures other than (or in addition to) transtelephonic monitoring; a hospital clinic normally performs an examination of the patient and a series of measurements of pacemaker function, often with the aid of noninvasive telemetry performed with the programming device. The clinics followed an average of 295 patients during 1989; the typical clinic size was 200 patients. The respondents followed a mean of 96 patients in their own private practice without the aid of an outside service; the median figure was 40 patients. Patients ordinarily visited the clinic twice during the year whether their pacemakers were single- or dual-chamber devices.

Transtelephonic monitoring was used by 68% of the respondents in their own private practice during 1989 (Figure 8). Of those who did not use this technique, 13% preferred clinic visits alone.

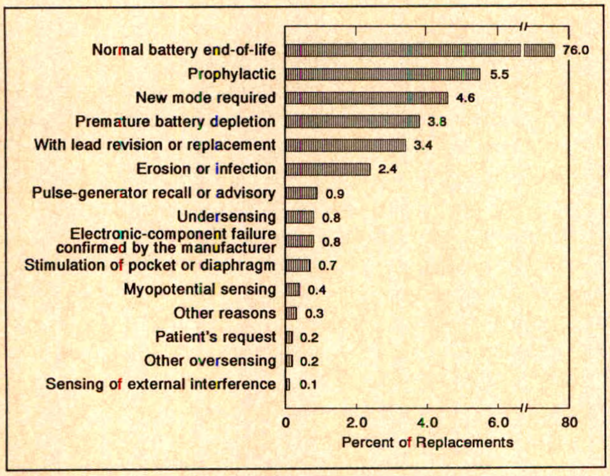

FIGURE 5. Indications for elective pulse-generator replacement.

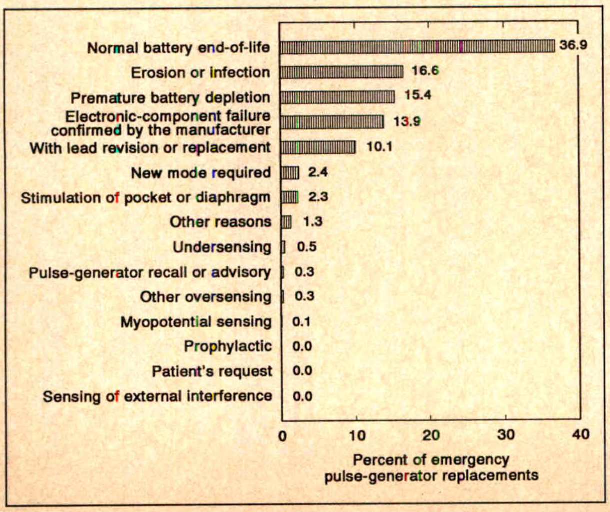

FIGURE 6. Indications for emergency pulse-generator replacement.

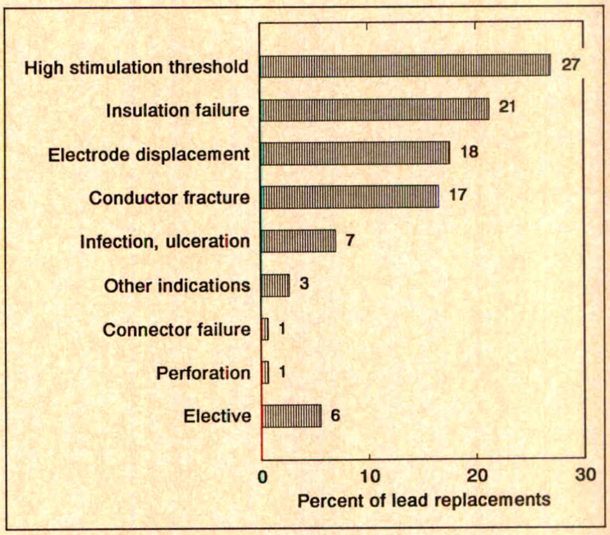

FIGURE 7. Indications for lead replacement.

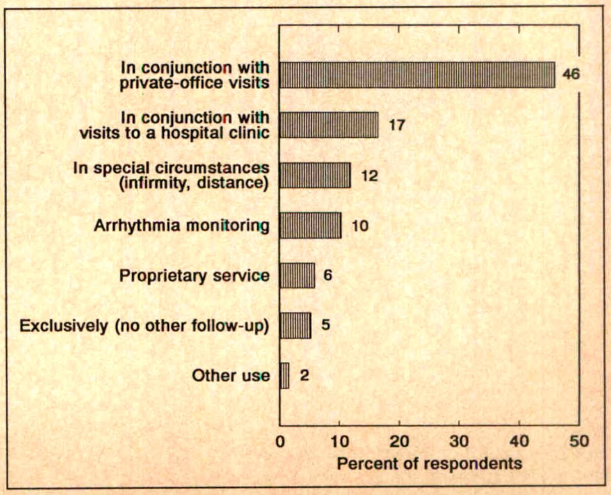

FIGURE 8. Use of transtelephonic monitoring in pacemaker follow-up during 1989.

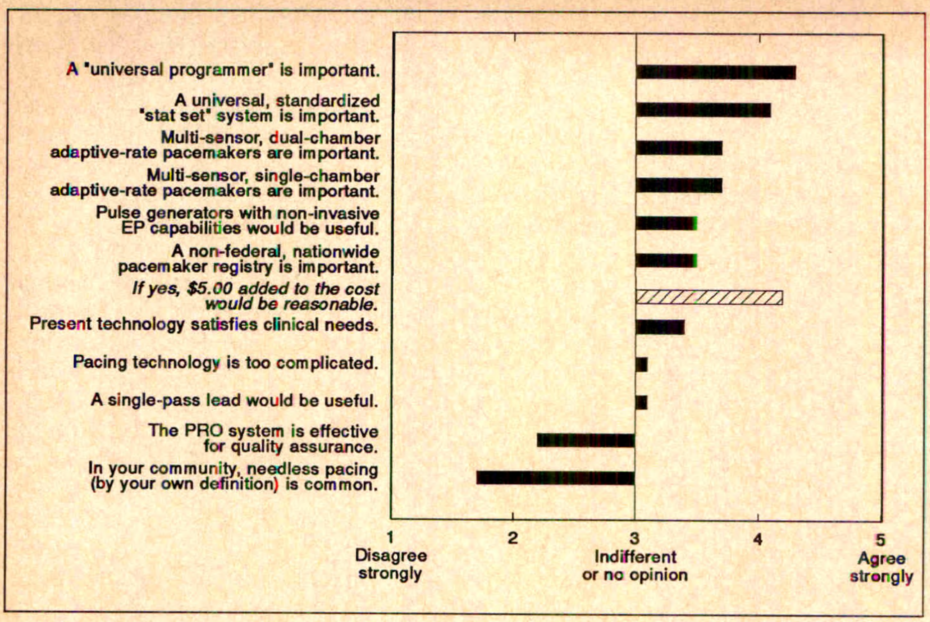

FIGURE 9. Respondents' opinions concerning several important issues. EP = electrophysiology; PRO = Professional Review Organization.

The most frequent reasons for file closure were death of known cause, not related to the pacemaker (54%), death of unknown cause (27%), and loss to follow-up (15%).

Respondents' opinions: Opinions were solicited on various pacing-related issues by means of a coding scheme (1 = agree strongly, 2 = agree, 3 = indifferent or no opinion, 4 = disagree, and 5 = disagree strongly). Programmable features of dual-chamber pacemakers on whose importance the respondents typically agreed strongly (5), as indicated by median codes, included lower and upper rate limits, output (stimulus amplitude duration, or both), atrial and ventricular sensitivity, and pacing mode. The respondents typically agreed (4) that electrogram and event-marker telemetry and active-fixation electrodes were important. Devices and techniques whose development the respondents typically agreed (4) was important included pulse generators lighter than 40 g, thinner than 8 mm, or both, multisensor single- and dual-chamber adaptive-rate pacemakers, "universal" pacemaker-programming devices, a "universally" accepted, standardized system for emergency ("stat set") programming of all new pacemakers, and the incorporation of noninvasive electrophysiologic study capabilities in implanted pulse generators. The respondents typically agreed (4) that pacing technology has advanced far enough to satisfy their clinical needs, but opinion was divided as to whether pacing technology has become more complicated than necessary for the needs of most patients. The responses concerning several other issues are summarized in Figure 9.

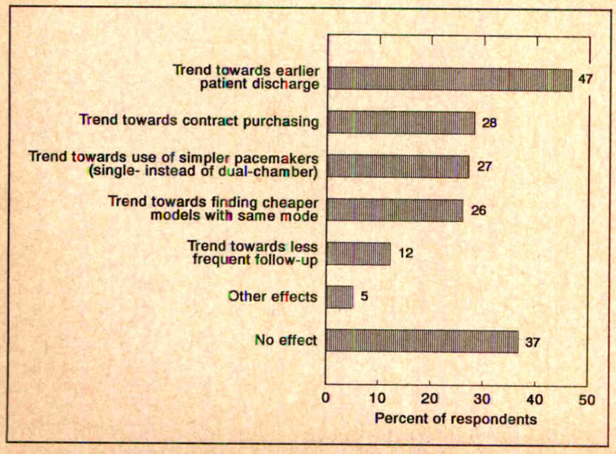

FIGURE 10. Effects of system of Diagnosis-Related Groups on the respondents' pacing practices.

The respondents reported that the impact of the system of Diagnosis-Related Groups had resulted in a trend toward earlier patient discharge and increases in the practice of contract purchasing, the use of single- instead of dual-chamber pacemakers, and the use of less expensive models with the same mode, as summarized in Figure 10, but more than a third reported that their pacemaker practice had not been affected. It was typically agreed (4) that the Professional Review Organization system was not an effective tool for quality assurance, that the Medicare guidelines for follow-up frequency were adequate, and that a nonfederal, nationwide registry of pacemaker implants similar to the European "Passport" registry[3] would be valuable and should be implemented even if a fee of $5.00 were added to the cost of every pacemaker.

DISCUSSION

Generally speaking, the 1989 Survey yielded no results that are particularly surprising to those deeply involved in pacing, conversant with recent technological developments and the results of their clinical application, and acquainted with the activities of the various cardiology, pacing, and electrophysiology societies. However, noteworthy trends and practice-pattern variations were identified, some related to the development of new technologies. Whereas the reasons for some differences are not clear, others can be understood more readily.

Implanter sample: As in many surveys, the respondents constituted a self-selected sample, in this case a group of physicians with sufficient interest and involvement in pacing to be willing to consult their records and fill in a 75-question document soliciting 320 items of data. Therefore, the analysis may well describe a somewhat more sophisticated group than pacemaker implanters in general, and certainly an influential one: the survey respondents (representing 7% of the nation's implanters) performed 14,152 primary pacemaker implantations during 1989 (16% of the nationwide total). For example, they performed a mean of 25 primary implantations during 1989, more than twice the mean primary implantation rate for the entire country (based on the manufacturers' estimates of 89,445 primary implantations performed by 7,919 implanters), which was only 11 pacemakers per implanter. Because a previous study found that physicians who performed <12 implantations per year experienced a higher incidence of complications than did more frequent implanters, this figure is somewhat disturbing.[1]

Pacemaker implantations: number and categories: A time profile of implantation frequencies for permanent pacemakers is shown in Figure 1 for the period beginning with the first U.S. Survey. The abrupt decrease in frequency beginning after 1981 was heralded by a report to the Senate Committee on Aging of fraudulent practices in the pacemaker industry,[4] which was soon followed by a report claiming that 22% of primary pacemaker implantations in Maryland during 1982 were needless,[5] and a subsequent report to the Senate Committee on Aging recommending changes in Medicare policies.[6] Although the claims of needless pacing were disputed,[7] the simultaneous appearance of these reports and the beginning of the trend may not have been merely coincidental. Other causes for this change may have been increased cost-consciousness, the publication of criteria for acceptable permanent pacing indications by the American Heart Association, the American College of Cardiology, and the North American Society of Pacing and Electrophysiology,[8,9] and, perhaps, the establishment of federally funded professional review organizations.[10] These considerations also may have contributed to the decreasing rate of growth in the use of dual-chamber pacemakers that began during the same period (Figure 4), although the decrease may also reflect a tendency to use adaptive-rate ventricular pacing (which became available at about that time) in circumstances where conventional dual-chamber pacing may be more appropriate.[11]

The proportion of implants represented by dual-chamber devices varies considerably among implanters and centers. (This proportion ranged from 0 to 100% for individual implanters; the standard deviation was 25%.) The choice of pacing mode is correlated also with medical specialty. VVI pacing was chosen in 53% of cases by surgeons and in 39% of cases by nonsurgeons ($p < 0.0001$). Surgeons tended to use single-chamber modes with or without rate modulation significantly more often than did nonsurgeons (74 vs 65%; $p = 0.0008$), and also chose single-chamber modes without rate modulation more often (40 vs 32%; $p = 0.0075$). They were less involved in follow-up (mean patients followed 62 vs 124; $p < 0.0001$), tended to perform less postoperative pacemaker programming (57 vs 77%; $p < 0.0001$), and, as mentioned earlier, to use bipolar electrode systems less frequently. Whether this relates to the overall practice patterns of busy surgeons in nonacademic centers, relative insensitivity to changing practice conventions in pacing, innate conservatism, or greater cost-consciousness, one can only speculate.

No recognized standard exists for selecting an appropriate mode in every situation, but with the expanding range of available pacing modes and pacemaker features, attempts are being made to identify the relevant criteria and clarify the decision-making process.[12]

The somewhat higher complication rates reported by implanters at academic centers may be due to the greater participation at such centers of residents and fellows working under the supervision of more experienced implanters, but it is also conceivable that more complications would be detected at such institutions because of closer scrutiny and attention to detail.

The degree to which implanters rely on a pacemaker manufacturer's sales representative for active assistance in pacemaker-implantation procedures (typically 80% of cases) is perhaps not widely recognized. It raises questions as to implanters' perceptions of their own skills, the availability of instrumentation and trained in-house technical staff, and matters of liability when problems occur.

The transition to long-lived lithium-chemistry batteries and the advent of more power-efficient circuits probably accounts for the decreasing proportion of pulse-generator replacements from 1979 to 1982 (Figure 2). The subsequent increase beginning in 1983 may be due at least in part to the increasing availability of DDD pacemakers that offer a more satisfactory option to patients who had symptoms of the pacemaker syndrome with single-chamber ventricular pacing.

Data more representative of the entire implanting population could perhaps be obtained by soliciting information from a single contact person from each center for all of the implanters at that center. Although this approach might yield more representative means of implantation rate, complication frequencies, indications, and so forth, it would not provide a basis for median calculations (for characterizing "typical" practices) or a way of soliciting individual implanters' opinions about pacing-related issues. Future pacing surveys might be conducted using a combination of the 2 methods, so that the questionnaires received by individual implanters could be briefer and less intimidating. This problem will not be resolved entirely by questionnaires, but could be alleviated markedly by the adoption of a nationwide pacemaker registry similar to the European "Passport" system.[3] That concept was supported by most of the respondents, who agreed that such a registry should be established even if an additional charge had to be added to the cost of each pulse generator.

Acknowledgment: We are pleased to express our thanks to Ronn Cort for able assistance in computer-entry and processing of the survey data.

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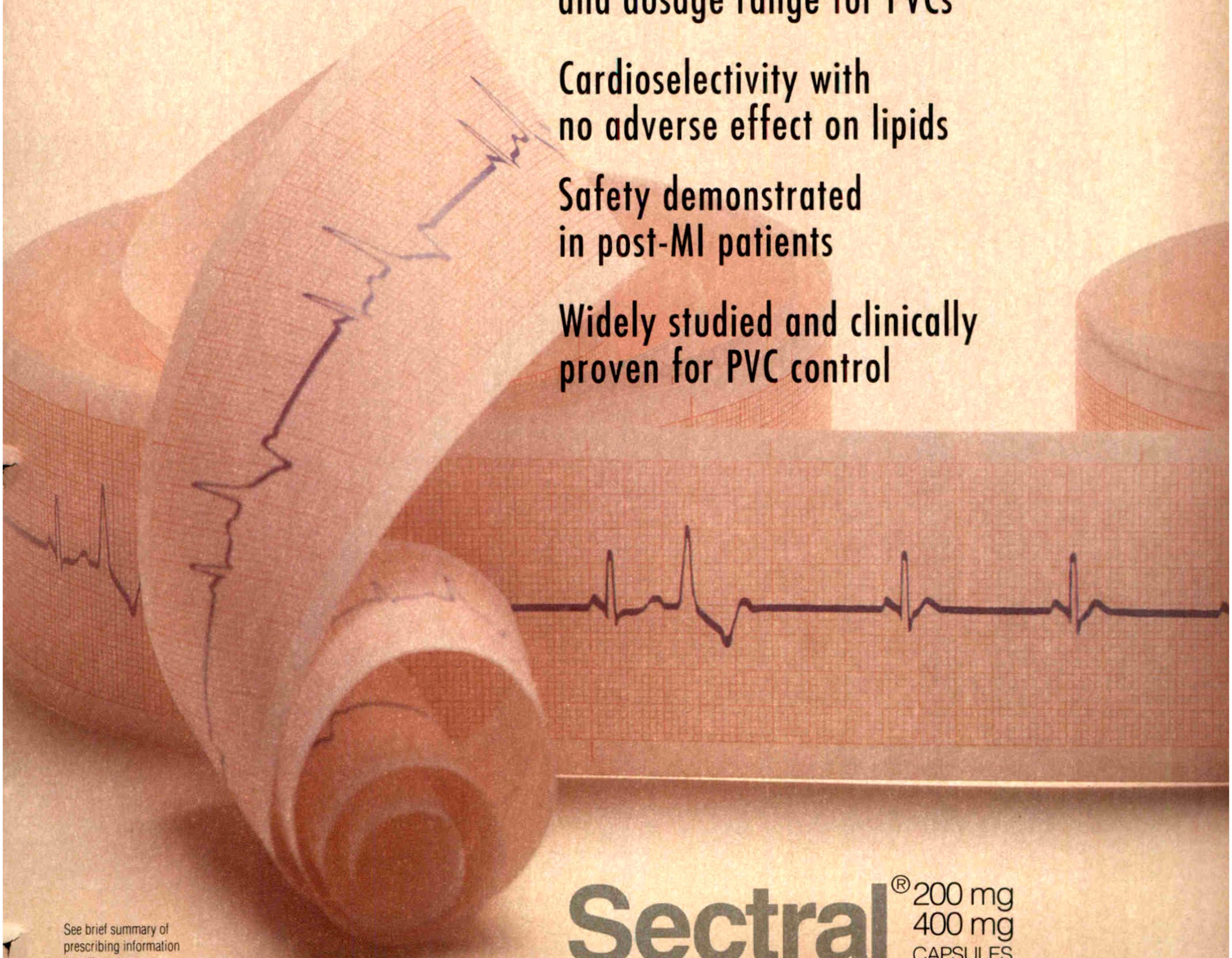

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CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuro-psychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Role of Sympathovagal Interaction in Diurnal Variation of QT Interval

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To elucidate the role of sympathovagal interaction in diurnal variation of QT interval, 24-hour ambulatory electrocardiographic recordings from 56 subjects (23 control subjects, 18 patients with atherosclerotic coronary artery disease, and 15 patients with diabetes mellitus) were studied. The QT interval at a heart rate of 60 beats/min (QT60) was determined for each of the day and night periods by regression analysis. Sympathetic and parasympathetic activities were assessed by spectral analysis of heart rate variability and represented by the low- and high-frequency components, respectively. The proportion of high-frequency component to the sum of low- and high-frequency components was used as an index of sympathovagal balance. The relative increase in QT60 at night (ΔQT60 [%]) was larger in control subjects (4.2 ± 2.1%) than in patients with coronary artery disease (2.2 ± 1.8%; $p < 0.01$) and diabetes mellitus (−1.5 ± 4.0%; $p < 0.001$). When the data from the 3 subject groups were pooled and analyzed, ΔQT60 was correlated with the change in the sympathovagal balance ($r = 0.554$; $p < 0.001$). Low-frequency component in the day alone was also related with ΔQT60 ($r = 0.554$; $p < 0.001$), but the ratio or difference of the high-frequency component value between day and night was not. These results indicate that although change in sympathovagal balance was responsible for the diurnal variation in QT interval, the enhanced sympathetic activity in the day was a major determinant of this phenomenon.

(Am J Cardiol 1992;69:339–343)

Impaired parasympathetic function is a predictor of poor outcome in patients with ischemic heart disease.[1–4] Therefore, it appears important to clarify the condition of cardiac autonomic function to identify high-risk patients. The recent advent of spectral analysis of heart rate variability has enabled sympathetic and parasympathetic cardiac functions to be studied separately.[5–9]

QT interval is longer in the night than in the day in healthy subjects, a phenomenon indicating diurnal QT variation.[10–12] Because transplanted hearts do not show this change in QT interval, diurnal changes in autonomic tone are considered responsible for this phenomenon.[11,12] Previous studies using pharmacologic interventions suggested that parasympathetic tone has a predominant effect on QT interval.[13–15] The involvement of sympathetic tone in the regulation of QT interval was indicated by other studies.[16–18] The purpose of the present study was to determine the contribution of each limb of the autonomic nerve system to diurnal QT variation by analyzing the power spectral components of heart rate variability.

METHODS

Study subjects: Fifty-six subjects (43 men and 13 women) who underwent 2-channel, 24-hour ambulatory electrocardiographic recording (Fukuda Denshi SM 26 and 28, Tokyo, Japan) were enrolled. The control group consisted of 23 healthy subjects. Eighteen patients with organic coronary artery disease (CAD) constituted the second group (1-vessel: 8; multivessel: 10). The third group comprised 15 patients with noninsulin-dependent diabetes mellitus (DM) in whom noninvasive studies did not reveal CAD. All subjects met the following criteria: (1) not receiving medication that could affect autonomic tone or QT interval, (2) sinus rhythm without apparent conduction disturbance, (3) normal electrolytes, and (4) normal left ventricular function (ejection fraction >0.5). Special care was taken to rule out DM in control subjects and patients with CAD. Structural heart disease other than CAD, history of myocardial infarction and invasive treatment for CAD was absent in patients with CAD.

Measurement of QT interval: Mean heart rates for every hour of the day (9 A.M. to 6 P.M.) and night (1 to 5 A.M.) were determined by computer system (SCM280, Fukuda Denshi, Tokyo, Japan). Electrocardiograms of approximately 10 seconds in duration were printed out at a paper speed of 25 mm/second every 10 minutes during the periods mentioned previously. Tracings with premature complexes were excluded from analysis. The QT interval was determined from the beginning of the QRS complex to the end of the T wave with stable iso-

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TABLE I Profiles of Subject Groups

	Control Subjects	CAD	DM	p Value
No. of pts.	23	18	15	
Age (yr)	55 ± 10	59 ± 12	58 ± 7	NS
Men/women	18/5	14/4	10/5	NS
Out/in	14/9	11/7	12/3	NS
QT60(day)	384 ± 22	400 ± 30*	398 ± 23	<0.05
QT60(night)	400 ± 20†	407 ± 30†	392 ± 15	NS

*p <0.05 vs control subjects; †p <0.001 vs QT60 (day).
Data are expressed as mean ± SD.
CAD = patients with coronary artery disease; DM = patients with diabetes mellitus; NS = not significant; Out/in = numbers of outpatients/inpatients.

electric line recording. The point at which the tangent drawn to the steepest portion of the downsloping T wave intersected the isoelectric line was used as the end of the T wave.[19] Means of 6 consecutive RR and QT intervals were used to represent each tracing.

QT intervals at a heart rate of 60 beats/min in the day (QT60<day>) and in the night (QT60<night>) were obtained separately by regression analysis. Three different regression formulas were used to minimize the bias associated with the method of regression analysis.[10,12,13,15,20–22] Fitting lines were expressed by the following formulas: (A) $[QT] = A + B \times [RR]$, (B) $[QT] = A + B \times \sqrt{RR}$, and (C) $[QT] = A + B \times \exp(-k \times [RR])$, where A, B and k are the regression parameters. Variability in QT interval was expressed as the relative increase in QT60 in the night normalized by QT60<day> (i.e., ΔQT60 [%] = [QT60<night> − QT60<day>]/QT60<day>).

Power spectral analysis of heart rate variability: The principles of data analysis have been described in earlier studies.[1,9] Briefly, after recordings were scanned on a computer system (SCM280, Fukuda Denshi), RR intervals were transferred to a personal computer system and analyzed using Holter data processing software (Version 1.033, Fukuda Denshi). A stationary section of 512 RR-interval values was selected from each 30 minutes of data. If a series of 512 consecutive RR intervals of good signal quality was not available, the data were abandoned. The computer calculated the power and frequency of every spectral component by a fast Fourier transformation method.[1] As illustrated schematically in Figure 1, a low-frequency component at 0.039 to 0.148 Hz and a high-frequency component at 0.148 to 0.406 Hz were determined.[1,5–9] Based on earlier studies,[1,5–9] low-frequency component was regarded as an index of sympathetic tone with vagal modulation, and high-frequency component as an index of parasympathetic tone. In all, 5 pairs of components were averaged to represent the autonomic activities of the day (low-frequency component<day> and high-frequency component<day>). The same procedures were repeated for the night RR intervals (low-frequency component<night> and high-frequency component<night>). The mean of the proportion of high-frequency component to the sum of low- and high-frequency components was used as an index of sympathovagal balance.

Statistics: Data are expressed as mean ± standard deviation. Intergroup differences in mean values were assessed by 1-way analysis of variance. The significance of differences in means between groups was determined by unpaired *t* test. The significance of differences in QT60 between day and night was assessed by paired *t* test. A p value <0.05 was considered significant.

RESULTS

Profiles of patient groups are presented in Table I.

Heart rate: Mean heart rate in the day was significantly higher in the DM group than in the CAD group (control 79 ± 4, CAD 74 ± 13 and DM 83 ± 9

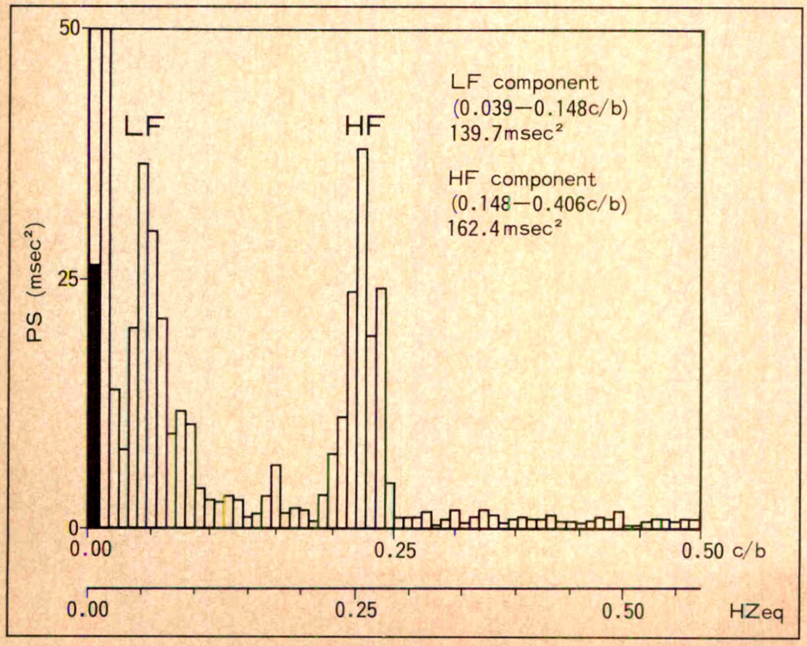

FIGURE 1. Example of histogram of power spectral (PS) density. *Abscissa* is frequency expressed both in cycles/beat (c/b) and equivalent Hz (HZeq) calculated from mean RR interval. HF = high-frequency; LF = low-frequency.

beats/min; p <0.001; CAD vs DM). There were no significant intergroup differences in the night (control 61 ± 7, CAD 63 ± 14 and DM 64 ± 9 beats/min).

Differences in QT60 according to the type of regression analysis: The r values derived from the 3 regression formulas for QT60 were (A) 0.81 ± 0.15, (B) 0.81 ± 0.14 and (C) 0.81 ± 0.15. QT60 calculated by formulas B and C were different from that calculated by formula A (2.0 ± 3.6 and 2.4 ± 3.6 ms, respectively). Because the differences among QT60s determined by different formulas were small, only data acquired by linear regression were used in the following analysis.

Comparison of QT60 and ΔQT60: QT60<day> and QT60<night> are shown for each group in Table I. QT60<day> was significantly higher in the CAD than in the control group (p <0.05). Representative relations between QT and RR intervals in a control subject and a CAD patient are shown in Figure 2. ΔQT60 in CAD patients (2.2 ± 1.8%) was smaller than that in control subjects (4.2 ± 2.1%; p <0.01; Figure 3). ΔQT60 in DM patients was the least among the 3 study groups (−1.5 ± 4.0%; p <0.001 vs control subjects, and p <0.01 vs CAD patients).

Power spectral analysis of heart rate variability: Power spectral densities of 2 components in each group are listed in Table II. Intergroup differences were significant for both low-frequency and high-frequency component<day> (p <0.001).

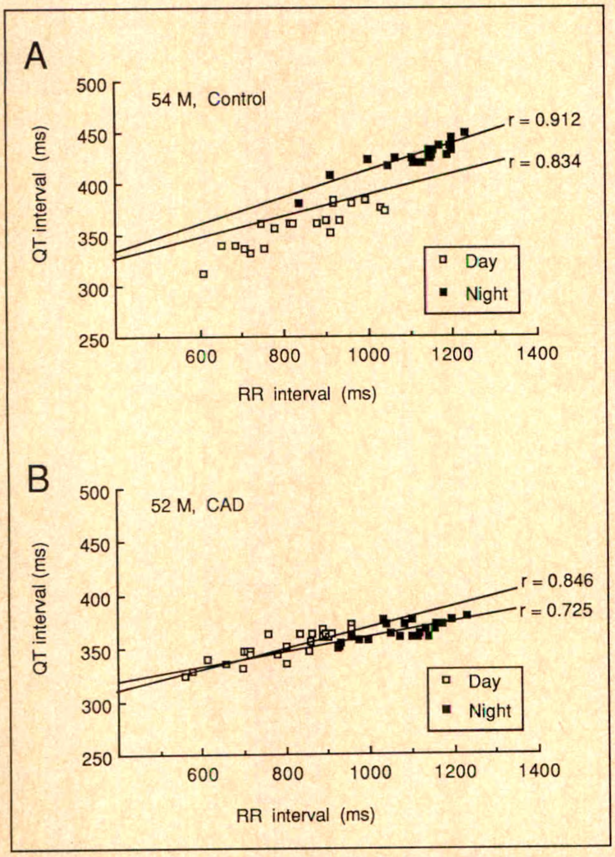

FIGURE 2. Relation between QT *(ordinate)* and RR *(abscissa)* intervals in day *(open squares)* and night *(closed squares)* in control subject and in patient with coronary artery disease (CAD). QT interval is longer in night than in day in *panel A*, whereas this diurnal QT variation is not noticeable in *panel B*.

TABLE II Low- and High-Frequency Components in Each Subject Group

	Control Subjects	CAD	DM	p Value
Day				
LF (ms^2)	286 ± 228	302 ± 336	73 ± 62*	<0.001
HF (ms^2)	128 ± 85	160 ± 152	64 ± 32*	<0.001
Night				
LF (ms^2)	194 ± 138	276 ± 408	198 ± 233	NS
HF (ms^2)	290 ± 243	303 ± 406	171 ± 158	NS

*p < 0.001 vs. control subjects and CAD.
Data are expresssed as mean ± SD.
HF = high-frequency component; LF = low-frequency component; other abbreviations as in Table I.

When the data from the 3 groups were pooled and analyzed ΔQT60 was not correlated with the change in high-frequency component between day and night alone (r = 0.164; Figure 4A). The ratio of high frequency component between day and night was not correlated with ΔQT60, either. Instead, the change in the proportion of high-frequency component to the sum of low- and high-frequency components between day and night (Figure 4B) showed a positive correlation with ΔQT60 (r = 0.554; p <0.001). Furthermore, ΔQT60 showed a significant correlation with the log value of low-frequency component<day> (r = 0.554; p <0.001; Figure 5). Neither low-frequency component<night>, high-frequency component<day>, nor high-frequency component<night> showed a relation with ΔQT60 like that of low-frequency component<day>.

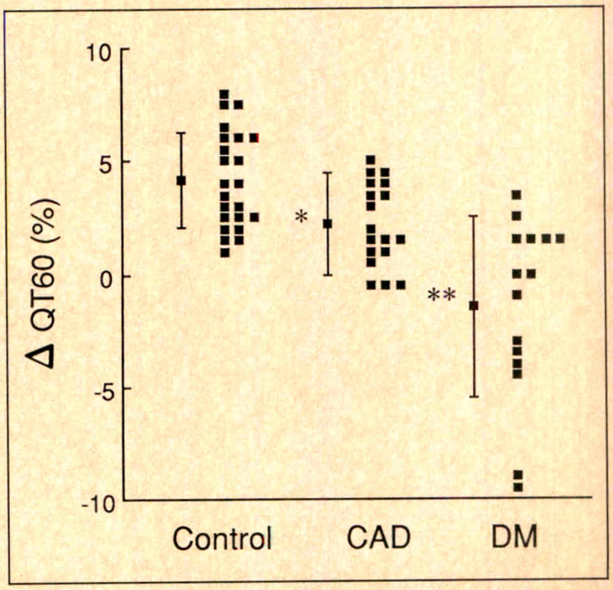

FIGURE 3. ΔQT60 (%) in 3 subgroups. *Closed squares with vertical bars* (standard deviation) indicate mean values of each group. CAD = patients with coronary artery disease; DM = patients with diabetes mellitus; * p <0.01 vs control subjects; ** p <0.001 vs control subjects and p <0.01 vs CAD.

DISCUSSION

The major findings of the present study were as follows: (1) In patients with CAD and DM, ΔQT60 was less remarkable than that in control subjects. (2) The diurnal change in sympathovagal balance assessed by the proportion of high-frequency component to the sum of low- and high-frequency components was correlated with ΔQT60. (3) Low-frequency component<day> alone was related with ΔQT60.

Earlier studies: In the earlier study by Ahnve and Vallin,[14] atropine caused a rate-independent reduction of QT interval, whereas propranolol did not cause significant change. In the subsequent study by Lecocq et al,[15] QT interval did not decrease during isoproterenol-induced tachycardia. In contrast, atropine-induced tachycardia produced changes similar to those resulting from exercise testing. They concluded that the physiologic relation between QT interval and heart rate was mainly under parasympathetic control. A bolus injection of isoproterenol,[17] and brief sympathetic nerve stimulation[16] prolonged QT interval under constant atrial pacing. When the intervention for β-adrenergic stimulation was continuous, QT interval was shortened.[15,16] Thus, the sympathetic effect on QT interval during daily activity may be complex.

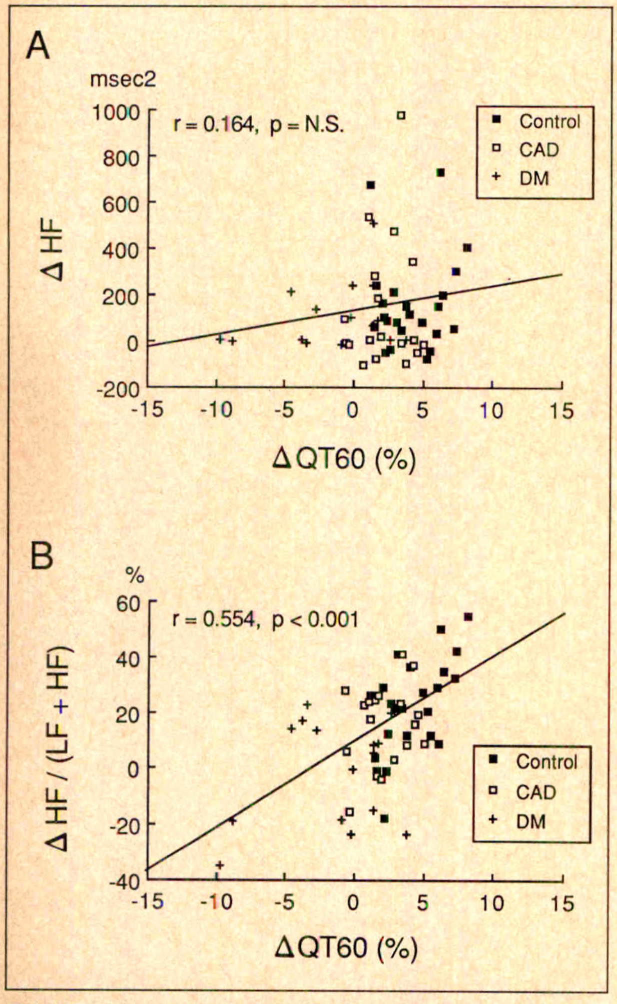

FIGURE 4. *A*, scatterplot of ΔQT60 and change in high-frequency component between day and night. *Abscissa* (ΔQT60 [%]) is the difference between QT60<night> and QT60<day> normalized by QT60<day>. *Ordinate* is net change in high-frequency component (ms^2) between day and night (ΔHF). There was no appreciable correlation between the 2 variables. *B*, scatterplot of change in high-frequency component/sum of low- and high-frequency components between day and night (ΔHF/[LF+HF], *ordinate*) and ΔQT60 (*abscissa*). Positive linear correlation existed between these 2 variables, suggesting that sympathovagal interaction was responsible for change in QT interval. Other abbreviations as in Figure 3.

Browne et al[10] first reported diurnal variation in the QT interval and speculated that increased vagal tone or sympathetic withdrawal, or both, was related to QT prolongation during sleep. Bexton et al[11] and Alexopoulos et al[12] demonstrated attenuated prolongation of QT interval in cardiac transplantation patients during sleep. However, earlier studies were not able to provide quantitative estimates of the effects of sympathetic and parasympathetic activities on QT interval.

Interpretation of the results: The high-frequency component of power spectral analysis of heart rate variability is a quantitative index of vagal cardiac function, whereas the sympathetic activity is reflected on the low-frequency component with parasympathetic modulation.[1,5–9] Neither the net change nor the ratio of high-frequency component between day and night was related with ΔQT60 (Figure 4A). Thus, diurnal variation in QT interval does not appear to be explained solely by the difference in parasympathetic activity between day and night. Instead, the diurnal QT variation appears to be a manifestation of the diurnal change in sympathovagal balance (Figure 4B). The present observations support the idea that sympathetic as well as parasympathetic tone regulates QT interval. Another interesting finding was that ΔQT60 was dependent on low-frequency component<day>. This indicates that enhanced sympathetic activity during the day played a major role

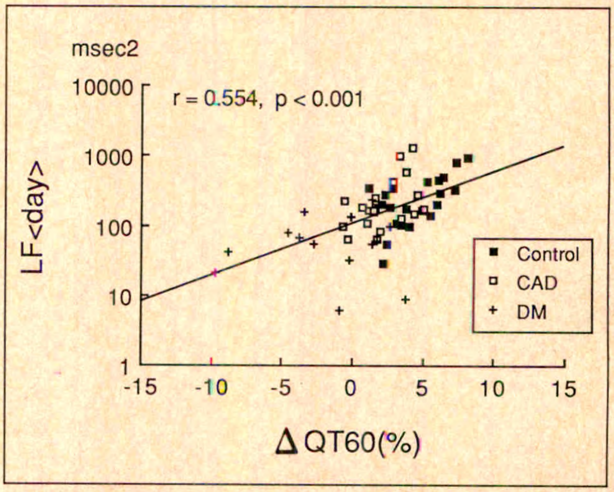

FIGURE 5. Scatterplot of ΔQT60 (*abscissa*) and low-frequency component<day> (LF<day>) (*ordinate*). Low-frequency component<day> is plotted on logarithmic scale. Positive correlation between the 2 variables suggests that sympathetic tone in day plays an important role in causing diurnal QT variation. Other abbreviations as in Figure 3.

in the diurnal change in sympathovagal balance, resulting in conspicuous diurnal QT variation.

Impaired parasympathetic function is frequently associated with CAD.[1-9,23-25] Hayano et al[8] disclosed that the reduction in vagal cardiac function was correlated with the angiographic severity of CAD. Like their study, most studies based on heart rate variability were performed at rest with controlled respiration at rest to quantify maximal or near maximal parasympathetic activity.[1,2,5,6,8,25] In the present study, QT interval and the power spectrum of heart rate variability were determined from 24-hour electrocardiographic recordings. Therefore, we could estimate only autonomic nerve activity in the uncontrolled state, not maximal activity. As shown in Table II, both low- and high-frequency components decreased in patients with DM, as was expected from earlier observations.[26-29] We considered that electrocardiograms recorded in the uncontrolled state could detect impaired autonomic function. The present observations suggest that in patients with CAD autonomic activities in daily life as well as maximal function differed from those in healthy subjects.

Methodologic considerations: The QT interval is a readily available variable and may be potentially useful in identifying subjects with impaired autonomic function within a large population. However, because diurnal variation in QT interval was significantly influenced by the low-frequency component<day>, the physical and mental activity of patients should be considered when categorizing them according to the state of autonomic nerve function. Because the range of heart rate during the day in patients with CAD was relatively low, we could not exclude the possibility that attenuated diurnal QT variation in these patients was caused by decreased physical activity rather than abnormal sympathovagal balance.

We analyzed the relation between QT interval and autonomic activities using pooled data from control subjects and patients with 2 different diseases. Because the concentrations of catecholamines were not measured in our study, and the sensitivity of the QT interval to humoral regulation may vary among patient groups, it is possible that factors other than autonomic nerve activities may have caused the intergroup differences in QT variation.

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Circadian Variation in Ventricular Arrhythmias in Hypertensive Men

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and Stephen B. Hulley, MD, MPH

Circadian patterns have been observed for various cardiovascular functions and events including sudden cardiac death. This study examined whether ventricular arrhythmias could be a pathophysiologic explanation for the increase in prevalence of sudden cardiac death observed between 6 A.M. and noon. Hypertensive men 35 to 70 years of age and without a history of symptomatic cardiac disease were withdrawn from diuretic treatment and received 1 month of oral electrolyte repletion with both 40 mmol of potassium chloride and 400 mg of magnesium oxide daily. Then continuous 24-hour Holter monitoring was performed and ventricular arrhythmias were classified by 6-hour time intervals. The interval from 6 A.M. to noon revealed a higher prevalence of complex or frequent ventricular arrhythmias than the interval from midnight to 6 A.M., as well as a higher mean number of ventricular premature complexes per hour. The differences were statistically significant (p <0.01) and amounted to increases of about one third. Ventricular arrhythmias during the other two 6-hour periods were intermediary in frequency. It is concluded that the increase in sudden cardiac death noted in the morning might be related, at least in part, to an increase in frequency of ventricular arrhythmias; the implications of this observation for preventive cardiology deserve further investigation.

(Am J Cardiol 1992;69:344–347)

Circadian variations for a number of hemodynamic parameters and cardiovascular events have been described. Studies have shown daily fluctuations in heart rate independent of physical activity[1] and fluctuations of systolic and diastolic blood pressure with lowest levels at 3 A.M. and highest at 10 A.M.[2] In patients with effort-induced angina, chest pain is most likely to occur between 6 A.M. and noon.[3] Nonfatal myocardial infarction[4] and sudden cardiac death[5] are also more likely to occur between 6 A.M. and noon than at other times of the day. These events may be temporally related to increases in platelet aggregability[6] resulting in platelet aggregation at the site of a thrombogenic arterial atherosclerotic lesion producing arterial occlusion. The increased prevalence of sudden cardiac death in the morning might also be related to variations in adrenal and sympathetic nervous system activity, or to other factors leading to an increase in ventricular arrhythmias.

Prior studies that have evaluated the circadian variation of ventricular arrhythmias have included large proportions of participants either after myocardial infarction or with angina[7–12] or participants selected because they had various cardiac disorders and >30 ventricular premature complexes (VPCs)/hour.[13,14] Some of these studies have shown a decrease in ventricular arrhythmias during sleep,[8–10,13,14] whereas others have not.[7,11,15] Little information is available on whether ventricular arrhythmias follow a circadian pattern in patients without a history of prior cardiac disease.

We evaluated the circadian variation in ventricular arrhythmias on 24-hour ambulatory electrocardiographic monitoring in hypertensive men who had been withdrawn from diuretic therapy and repleted with oral potassium and magnesium for 1 month. Men with a prior history of angina or myocardial infarction were eliminated from analysis. This study design enabled us to evaluate the circadian variation in ventricular arrhythmias in an asymptomatic population free of electrolyte abnormalities or clinical cardiac disease.

METHODS

Background and design overview: Details of the study design and selection process have been presented previously.[16] Briefly, the Hypertension Arrhythmia Reduction Trial is a clinical trial designed to assess the frequency and severity of ventricular arrhythmias associated with the use of various diuretic combinations. Hypertensive men with electrocardiographic abnormalities at rest were selected for the study subjects because the Multiple Risk Factor Intervention Trial suggested that they may be especially at risk for sudden death

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with diuretic use. The portion of the study described in this report was performed after diuretic withdrawal and electrolyte repletion (see later). The study group was recruited both from clinical populations and by a direct mail campaign. Subjects were included in the study if they had been taking diuretics for ≥ 6 months and their diastolic blood pressure was <95 mm Hg, or if they had not been taking diuretic therapy but had a history of hypertension and were either taking nondiuretic antihypertensive drugs or had a diastolic blood pressure ≥ 90 mm Hg but <105 mm Hg. All subjects gave informed consent and the study design was explained to the subjects' physicians.

We excluded men who were taking medications that might influence the development of ventricular arrhythmias such as antiarrhythmic drugs, β blockers, theophylline preparations, digitalis preparations, phenothiazines and tricyclic antidepressants. Other antihypertensive medication not often associated with arrhythmias, such as methyldopa, clonidine, enalapril or prazosin, were not a basis for exclusion and were continued at a constant dosage throughout the study. We excluded men with a history of myocardial infarction, congestive heart failure, angina pectoris, renal insufficiency (creatinine >2.0 mg/dl), or other serious illness including psychiatric disability, or inability or unwillingness to give informed consent.

The men were withdrawn from diuretic treatment and all participants received 1 month of oral electrolyte repletion with both 40 mmol of potassium chloride and 400 mg of magnesium oxide (containing 241.3 mg of elemental magnesium) daily. Serum potassium and magnesium were then measured and a continuous 24-hour Holter monitoring test performed.

Continuous Holter monitoring: Continuous 24-hour Holter monitoring was performed using the Cardiotechorder III dual lead system. The electrocardiogram was recorded continuously on tape using a cassette system. Tapes were sent to Cardio Data Systems (Haddonfield, New Jersey) for analysis. Whole tapes were printed at high speed on recording paper using the Cardio Data Corporation Mark IV Holter Analyzer. Specific areas of interest, identified by irregularity in the QRS pattern, were printed at real time and evaluated by an analyst. Ventricular arrhythmias were classified in a manner similar to that of Lown et al,[17] according to the presence of the following arrhythmia types: VPCs, multiform extrasystoles, ventricular couplets, ventricular tachycardia and R-on-T VPCs.[17] We created a summary category of the presence of a frequent (≥ 30 VPCs/hour) or a complex (presence in 24 hours of any of the following: multiform extrasystoles, ventricular couplets, ventricular tachycardia, or R-on-T VPC) ventricular arrhythmia for at least 1 of 24 hours. The precision of these measurements is indicated by their within-individual correlation of ventricular arrhythmias on continuous 24-hour Holter monitoring before and after diuretic treatment; kappa coefficients for the whole cohort were 0.74 (95% confidence interval = 0.61, 0.88) for the presence of ≥ 30 VPCs/hour, and 0.47 (95% confidence interval = 0.33, 0.60) for the presence of a frequent or complex ventricular arrhythmia.

TABLE I Characteristics of Study Sample

Characteristic	Frequency
Number in cohort	199
Mean age (years)	61 (8)
Race	
Asian	5%
Black	15%
Hispanic	5%
Indian	0.5%
White	74%
Other	1%
Systolic blood pressure (mm Hg)*	145 (17)
Diastolic blood pressure (mm Hg)*	87 (10)
Pulse*	71 (11)
Body surface area (m^2)*	1.9 (0.2)
Serum potassium (mEq/liter)*	4.3 (0.4)
Serum magnesium (mEq/liter)*	2.0 (0.2)
Cigarettes	
Current	18%
Past	55%
Never	27%
Antihypertensive other than diuretic	33%

*Mean (standard deviation).

Statistical analysis: Ventricular arrhythmias and mean heart rate were recorded every hour for a 24-hour period. The proportion of participants with a specific ventricular arrhythmia in at least 1 hour of each 6-hour time block, 6 A.M. to noon, noon to 6 P.M., 6 P.M. to midnight, and midnight to 6 A.M., was determined. Additionally, mean heart rate and mean single VPCs/hour were also calculated for the 6-hour time blocks. Hour by hour frequency of ≥ 30 VPCs and frequent or complex ventricular arrhythmias were examined.

The analysis comparing the risk of having a specific ventricular arrhythmia at a given time of day to the risk from 6 A.M. to noon was performed using a method that takes into account the within-person correlation among outcomes (arrhythmias over time) for each participant. This approach, based on generalized linear models, regards the correlation among multiple observations on the same individual as a "nuisance" parameter.[18] We used a logit function to estimate the regression coefficients and their standard errors, and we used an exchangeable correlation matrix that assumes correlations, which represent the weighted average correlation among observed outcomes, are similar over time.[19,20] Associations for dichotomous outcomes are presented as odds ratios with 95% confidence intervals. Coefficients and their standard errors are presented for continuous outcomes. Statistical analysis was performed using SAS (Statistical Analysis System) software on an IBM 4341 mainframe computer.[21]

RESULTS

Study sample: Clinical characteristics of the study sample are listed in Table I. The study sample included 199 men (mean age 61 years). Mean serum potassium was 4.3 mEq/liter and mean serum magnesium was 2.0 mEq/liter, indicating successful repletion of these electrolytes.

Circadian variation of ventricular arrhythmias: The frequency of participants having ventricular arrhyth-

TABLE II Proportion of Participants with Arrhythmias in at Least One Hour in the Six-Hour Time Interval

Hour	Single VPC (%)	Pair (%)	VT (%)	MF (%)	>10 VPCs (%)	>30 VPCs (%)	F/C (%)	Mean HR
6 A.M.–noon	70	12.1	3.0	27	26	17	34	80
Noon–6 P.M.	70	10.1	3.0	24	26	16	29	83
6 P.M.–midnight	62	9.5	2.5	23	26	18	29	77
Midnight–6 A.M.	58	5.5	2.0	20	20	11	26	66

Hour	Mean VPCs (%)
6 A.M.–noon	30
Noon–6 P.M.	32
6 P.M.–midnight	28
Midnight–6 A.M.	17

F/C = frequent or complex arrhythmia defined as presence of any of the following: ≥30 VPCs/hour or any of the following grades: HR = heart rate; MF = multiform extrasystole VPC; Pair = presence of ventricular couplet; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

TABLE III Risk of Ventricular Arrhythmias per Hour by Time of Day Compared with 6 A.M. to Noon

	Time	Odds Ratio	95% CI	p Value
≥30 Single VPCs	Noon–6 P.M.	0.96	(0.73, 1.27)	0.37
	6 P.M.–midnight	1.07	(0.82, 1.41)	0.28
	Midnight–6 A.M.	0.63	(0.46, 0.85)	<0.01
Pair	Noon–6 P.M.	0.81	(0.53, 1.25)	0.17
	6 P.M.–midnight	0.77	(0.50, 1.18)	0.11
	Midnight–6 A.M.	0.43	(0.24, 0.77)	<0.01
VT	Noon–6 P.M.	1.00	(0.34, 2.90)	0.50
	6 P.M.–midnight	0.83	(0.24, 2.81)	0.38
	Midnight–6 A.M.	0.66	(0.18, 2.41)	0.26
Multiform VPC	Noon–6 P.M.	0.85	(0.63, 1.15)	0.15
	6 P.M.–midnight	0.83	(0.64, 1.08)	0.08
	Midnight–6 A.M.	0.69	(0.51, 0.94)	<0.01
F/C*	Noon–6 P.M.	0.81	(0.62, 1.06)	0.06
	6 P.M.–midnight	0.81	(0.63, 1.04)	0.05
	Midnight–6 A.M.	0.70	(0.52, 0.93)	<0.01
	Time	**Beta**	**95% CI**	**p Value**
Mean VPCs	Noon–6 P.M.	2.2	(−4.5, 8.9)	0.26
	6 P.M.–midnight	−2.6	(−10.6, 5.4)	0.26
	Midnight–6 A.M.	−13.1	(−23.1, −3.1)	<0.01

*See legend to Table II.
CI = confidence interval.

mias in at least 1 hour during the 4 different time intervals is presented in Table II. Participants were less likely to have any category of ventricular arrhythmia in the time period from midnight to 6 A.M. including ventricular couplets, ventricular tachycardia, multiform ventricular extrasystoles, and frequent VPCs. The mean number of VPCs/hour was also lowest during this time.

Figure 1 presents the hour-by-hour frequency of participants with a frequent or complex ventricular arrhythmia, as well as the percentage of participants with ≥30 VPCs/hour. There is a consistent pattern of less ventricular arrhythmias between midnight and 6 A.M. than during other times of the day.

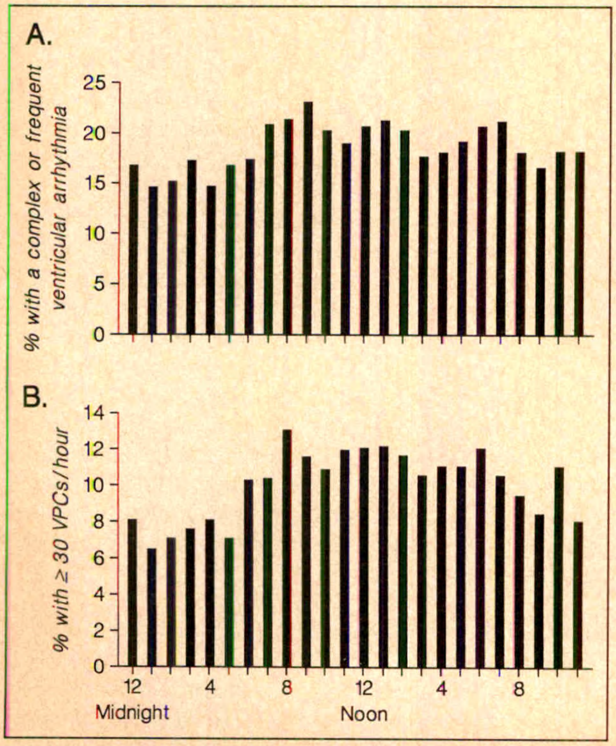

FIGURE 1. Prevalence by time of day of participants with a complex or frequent ventricular arrhythmia *(A.)* or ≥30 ventricular premature complexes (VPCs)/hour *(B.)*.

Statistical analysis comparing each of the other three 6-hour time intervals with the interval from 6 A.M. to noon revealed that participants were more likely to have any type of complex or frequent ventricular arrhythmia in this period ($p < 0.01$) than in the time period from midnight to 6 A.M. with the exception of ventricular tachycardia where the trend is in this direction (Table III). The mean number of VPCs/hour are also greater from 6 A.M. to noon than from midnight to 6 A.M. The results were similar after adjusting for heart rate and use of other hypertensive medication.

DISCUSSION

Myocardial infarction and sudden death do not occur randomly throughout the day, but rather in a circadian pattern with a morning increase in frequency.[5,22] A variety of physiologic processes such as heart rate, coronary blood flow, systemic pressure, platelet aggregability, plasma cortisol, tissue-type plasminogen activity, and plasma epinephrine have a similar pattern.[22] Our finding that ventricular arrhythmias become more prevalent when patients go from sleep to awakening is consistent with these observations. Increased activity of the sympathetic nervous system in the morning may increase electrical instability of the myocardium.[23,24] The pattern of hourly frequency of ventricular arrhythmias presented here is remarkably similar to the report of the time of day of out-of-hospital sudden cardiac death in a study of 2,203 patients dying in Massachusetts in 1983.[5]

Ventricular arrhythmias play an important role in the pathophysiology of sudden death.[25,26] Studies have shown that finding VPCs on the electrocardiogram at rest or on 24-hour electrocardiographic monitoring is associated with a significant increase in mortality, particularly in patients with a prior myocardial infarction.[25-27] The risk of sudden death appears to increase with high grade (Lown classes) versus low grade VPCs.[28-30] In the Multiple Risk Factor Intervention Trial, those who had frequent or complex ventricular arrhythmias on a 2-minute electrocardiogram at rest had a relative risk of sudden cardiac death of 4.2 compared with those participants without ventricular arrhythmias.[31] The finding that there is an acute increase of ventricular arrhythmias in the morning suggests that the increase in sudden cardiac death noted in the morning might be related, at least in part, to an increase in ventricular arrhythmias.

Prior studies that have evaluated the circadian variation of ventricular arrhythmias have included large proportions of participants with various cardiac disorders.[7-14] Since sudden cardiac death frequently occurs in patients without a prior history of cardiac disease, it is important to determine if these people are also at an increased risk for ventricular arrhythmias in the morning. In our study, men with a prior history of angina or myocardial infarction were eliminated from analysis and participants were repleted with potassium and magnesium to avoid the potential effects of deficiencies in these electrolytes on ventricular arrhythmias. The findings of a decrease in both the frequency of VPCs as well as the prevalence of complex ventricular arrhythmias during sleep with an increase on awakening are consistent with prior studies and extend these findings to men without symptomatic cardiac disease.

The eventual goal of any observation is to alter processes that contribute to disease events. Thus, therapies that modify morning peaks in blood pressure, heart rate, vasoconstriction, blood coagulability and catecholamine and cortisol levels might reduce the development of ventricular arrhythmias and sudden cardiac death. However, although the peak incidence of ventricular arrhythmias and sudden cardiac death is from 6 A.M. to noon, most events occur at other times of the day, and their prevention necessitates a broader approach. The major significance of our findings is the support they lend to the notion that disease onset may be triggered by physiologic processes that are susceptible to interventions.

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Effects of a Single Oral Dose of Captopril on Left Ventricular Performance in Severe Mitral Regurgitation

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For comparable decreases in systemic resistance, angiotensin-converting enzyme inhibitors produce a lesser increase in cardiac output than do previously used vasodilators. Although the reason for this is not yet clear, the possibility of a negative inotropic effect of angiotensin-converting enzyme inhibitors was demonstrated by intracoronary injection. The effects of an oral dose of captopril on systolic performance were assessed by examining left ventricular (LV) pressure-volume loops obtained with simultaneous cineangiography and micromanometer pressure recordings before and 90 minutes after administration of oral captopril (25 to 50 mg) in 18 patients with chronic, severe mitral regurgitation. Group 1 (n = 9) was given captopril alone, and group 2 (n = 9) was given captopril plus atropine (0.04 mg/kg intravenous) to assess the role of parasympathetic activity in mediating the effects of captopril. Captopril reduced heart rate (90 to 81 beats/min; $p < 0.002$) and LV end-diastolic pressure (13 to 10 mm Hg; $p = 0.03$), despite a slight increase in end-diastolic volume (257 to 264 ml; p = not significant) that suggests improved diastolic properties. Despite a decrease in end-systolic pressure (103 to 90 mm Hg; $p < 0.001$), ejection fraction did not increase (0.60 to 0.58; p = not significant) owing to an increase in end-systolic volume (107 to 114 ml; $p = 0.008$). Contractile performance, estimated from the end-systolic pressure/volume quotient, was consistently depressed by captopril, as was the relation of preload-corrected ejection fraction to end-systolic stress. Pretreatment with atropine (group 2) did not block the effects of captopril on LV volumes and contractile performance. Thus, in patients with chronic, severe mitral regurgitation, a single oral dose of captopril has a negative inotropic effect (not parasympathetically mediated) that blunts the anticipated increase in ejection performance.

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For comparable decreases in systemic resistance, angiotensin-converting enzyme inhibitors produce a lesser increase in cardiac output in patients with cardiomyopathy than do previously used vasodilators.[1,2] The reason for this deficit in cardiac output has not been fully clarified. One contributing factor may be a decrease in heart rate with angiotensin-converting enzyme inhibitors.[1,2] A second possible factor may be a negative inotropic effect, as demonstrated by Foult et al[3] using intracoronary enalaprilat. There are preliminary data that suggest that angiotensin-converting enzyme inhibitors may have disparate effects on systolic and diastolic myocardial properties, which result in improved diastolic but not systolic left ventricular (LV) performance.[4] In view of these findings and the fact that the usefulness of angiotensin-converting enzyme inhibitors in regurgitant valve lesions has not been established, we evaluated the effect of a single oral dose of captopril on LV performance in 18 patients with chronic, severe mitral regurgitation (MR). This is a disorder in which vasodilator therapy has particular appeal,[5,6] but in which there are few data regarding the effects of therapy with angiotensin-converting enzyme inhibitors. Having found evidence of a negative inotropic effect of captopril, we attempted to determine if this effect may be parasympathetically mediated.[7]

METHODS

Subjects: From our population of patients with valvular heart disease, we recruited for this study those with severe (by angiography and Doppler color flow mapping), nonischemic MR in normal sinus rhythm who were considered candidates for valve surgery based on the presence of either symptoms or LV dysfunction, and who were aged ≥15 years and did not have any serological evidence of active rheumatic carditis. The latter is the most common etiology for MR at Baragwanath Hospital. Between August 1989 and October 1990, 18 consecutive such patients were identified. Written consent was obtained after a description of the protocol, which was approved by the ethics committee of the University of Witwatersrand, was read to the patient (and guardian for those aged <21 years) in his/her own language. Evaluation before catheterization included 2-dimensional echocardiography and color Doppler recordings, by which all patients were diagnosed with severe MR. The etiology of MR was due to rheumatic disease (n = 12), ruptured chordae (idiopath-

TABLE I Effect of Captopril Without (group 1) and With (group 2) Atropine

	Group 1		Group 2		p Value	
	Before	After	Before	After	Captopril	Atropine
Heart rate (beats/min)	90 ± 18	81 ± 17	107 ± 8	103 ± 8	0.000	0.065
Systemic resistance (dynes · s · cm^{-5})	2,237 ± 662	1,840 ± 537	2,085 ± 490	2,130 ± 432	0.068	0.04
End-systolic pressure (mm Hg)	103 ± 10	90 ± 9	108 ± 18	95 ± 11	0.001	NS
End-systolic stress ($kdyn/cm^2$)	205 ± 73	178 ± 65	214 ± 105	209 ± 64	0.06	NS
End-diastolic pressure (mm Hg)	13 ± 8	10 ± 6	8 ± 6	7 ± 7	0.03	NS
End-diastolic volume (ml)	257 ± 79	264 ± 79	258 ± 86	256 ± 93	NS	NS
End-systolic volume (ml)	107 ± 56	114 ± 54	121 ± 40	129 ± 47	0.008	NS
Ejection fraction	0.60 ± 0.14	0.58 ± 0.12	0.53 ± 0.08	0.49 ± 0.08	NS	NS
Regurgitant fraction	0.72 ± 0.10	0.70 ± 0.11	0.73 ± 0.12	0.71 ± 0.17	NS	NS
End-systolic pressure/volume quotient (mm Hg/ml)	1.37 ± 0.98	0.98 ± 0.52	0.99 ± 0.37	0.82 ± 0.28	0.003	NS

NS = not significant.

ic [n = 1], healed endocarditis [n = 1]) and probable myxomatous (n = 4). Mitral valve area was >2 cm^2 in all patients, as measured by 2-dimensional echocardiography or Doppler pressure half-time.

Although the exact duration of the MR could not be determined, no patient presented with abrupt onset of symptoms (<4 weeks), and all had either LV or left atrial enlargement, or both, suggesting that the MR was not acute. In patients who were undergoing oral captopril therapy, the drug was stopped ≥2 days before catheterization. In group 1, 5 patients were receiving long-term angiotensin-converting enzyme inhibitor therapy up to 2 (n = 1) or 3 (n = 4) days before the study; in group 2, 5 patients were undergoing therapy up to 2 to 8 days before the study. Diuretics were continued until the evening before catheterization. Digoxin was not used. None of the patients had an elevated serum creatinine or low serum sodium.

Patient groups: Patients were sequentially allocated in a nonblinded fashion to 1 of 2 groups: group 1 (n = 9) was treated with oral captopril alone, and group 2 (n = 9) was pretreated with intravenous atropine before captopril administration. Mean ages for groups 1 and 2 were similar (30 ± 12 vs 32 ± 11 years; p = not significant [NS]), as were body surface (1.65 ± 0.26 vs 1.51 ± 0.15 m^2; p = NS) and echocardiographic mitral valve (5.4 ± 3.0 vs 4.2 ± 1.1 cm^2; p = NS) areas. A rheumatic etiology was present in 4 patients in group 1 and in 8 in group 2. New York Heart Association functional class was 2.9 ± 0.6 in group 1 and 2.6 ± 0.8 in group 2. An untreated control group was comprised of 5 patients (aged 41 ± 11 years, body surface area 1.67 ± 0.25 m^2) who also had isolated severe MR.

Procedure: Patients were premedicated with promethazine (25 mg intramuscular) and pethidine (25 mg intramuscular). Right heart catheterization was performed through the femoral vein with a thermodilution flotation catheter. Left-sided heart catheterization was performed retrograde through the femoral artery using an 8Fr micromanometer catheter with a pigtail configuration.

After measuring right and left heart hemodynamics, atropine (0.02 mg/kg) was given intravenously to patients in group 2, 10 minutes before LV cineangiography. Meglumine ioxaglate (40 to 50 cc) was injected into the left ventricle during biplane cine (30 right and 60 left anterior oblique). The first contrast injection was performed after atropine administration in group 2 and before the precaptopril measurements in both groups so that there would be no contrast injections between the pre- and postcaptopril measurements, thus minimizing the possible effects of contrast on interpretation of the data. The injection was gated to diastole using the electrocardiogram to reduce the induction of ectopic beats. LV pressure was recorded from the micromanometer catheter at 100 mm/s paper speed during LV cineangiography. Precise synchronization between pressure and cineangiography was achievable with a cineframe marker that records a mark for each film exposure (60/second) simultaneous with the pressure recording and records the frame number on the film with a diode simultaneous with the marks on the pressure recording. After a 15-minute interval to allow effects of contrast to dissipate, baseline hemodynamics were recorded in triplicate at 10-minute intervals.

Captopril was then given orally at a dose of 25 mg to patients with body surface areas <1.7 m^2 (n = 15) and at a dose of 50 mg to larger ones (n = 3). Hemodynamics were observed continuously. At 90 minutes, when angiotensin-converting enzyme inhibition activity reaches a peak,[8] measurements were again repeated in triplicate at 10-minute intervals. These measurements were preceded by administration of another 0.02 mg/kg of atropine (total dose 0.04 mg/kg) to group 2. Since there was a slight attenuation in the hemodynamic effects of captopril after 90 minutes, only the 90-minute values are listed in Table I. LV cineangiography with simultaneous micromanometer LV pressure recordings was then performed using the same injection protocol, and image intensifier and table positions as for the baseline study.

There were no complications, and no side effects of captopril were reported by the patients.

Analysis of catheterization data: LV silhouettes for each frame of the first well opacified beat of each LV cine not preceded by an ectopic beat were digitized using a handheld cursor. LV wall thickness was measured at the midthird of the anterior wall in the right anterior oblique view for the end-diastolic frame. Correction factors for ventricular measurements were derived from the grids positioned at the center of the ventricle. LV volume was computed using the area-length method and a regression equation.[9] Because the silhouette borders in the left anterior oblique view were sometimes unclear over the spine and diaphragm, and because segmental dyssynergy was absent, volumes were computed from the single plane right oblique view. LV pressure for the corresponding cardiac cycle was digitized using a handheld cursor interfaced with a computer.

LV volume and pressure were computer-plotted frame-by-frame. To make the volume-time waveform analysis as objective as possible, the data were fit to ninth- to eleventh-order polynomial equations using a Marquardt curve-fitting program. End-diastolic volume was located as the maximal volume, and end-systolic volume as the minimal volume where the rate of volume change became 0. The angiographic (total) stroke volume was computed as the difference between end-diastolic and end-systolic volumes. Forward stroke volume was computed from the thermodilution cardiac output and the heart rate. Although mixed venous and arterial saturations were also obtained to enable calculation of Fick outputs (using an assumed molecular oxygen consumption), the thermodilution outputs were used since no patient had evidence on combined echocardiography and Doppler color flow mapping or on physical examination of more than mild tricuspid regurgitation.

Regurgitant fraction was computed from the quotient: (total–forward stroke volume)/total stroke volume. The end-systolic pressure/volume quotient was obtained from the digitized pressure-volume loops using a method previously described[10] that objectively locates the upper left "corner" of the loop.

Systolic and diastolic wall stress were computed and used as previously described[10] to estimate preload corrected ejection fraction as a measure of relatively load-independent LV systolic performance.

Data are reported as mean ± SD. A commercially available statistics program[11] was used to perform 2-way analysis of variance for repeated measures to detect time (during measurements at 10-minute intervals), captopril and atropine effects. Differences between measurement intervals were isolated with the Tukey test. Baseline hemodynamics measured in triplicate remained stable by repeated measures analysis of variance over the 20-minute baseline observation period before administration of captopril, and the 3 measurements at 90, 100 and 110 minutes after captopril were therefore compared with the average of the 3 baseline measurements.

RESULTS

As shown in Table I, heart rate, LV end-systolic pressure, systemic resistance and end-systolic wall stress were decreased 90 minutes after administration of captopril, although the decreases in the latter 2 parameters were not statistically significant. Mean arterial pressure decreased from 90 ± 7 to 73 ± 9 mm Hg in group 1 and from 88 ± 4 to 82 ± 9 mm Hg in group 2 ($p < 0.001$ for captopril effect, and $p < 0.01$ for atropine effect). Despite the decrease in end-systolic pressure, there was a modest but significant increase in end-systolic volume instead of the expected decrease. LV end-diastolic pressure decreased, but end-diastolic volume did not. Neither ejection fraction nor regurgitant fraction improved after captopril. Percent changes from

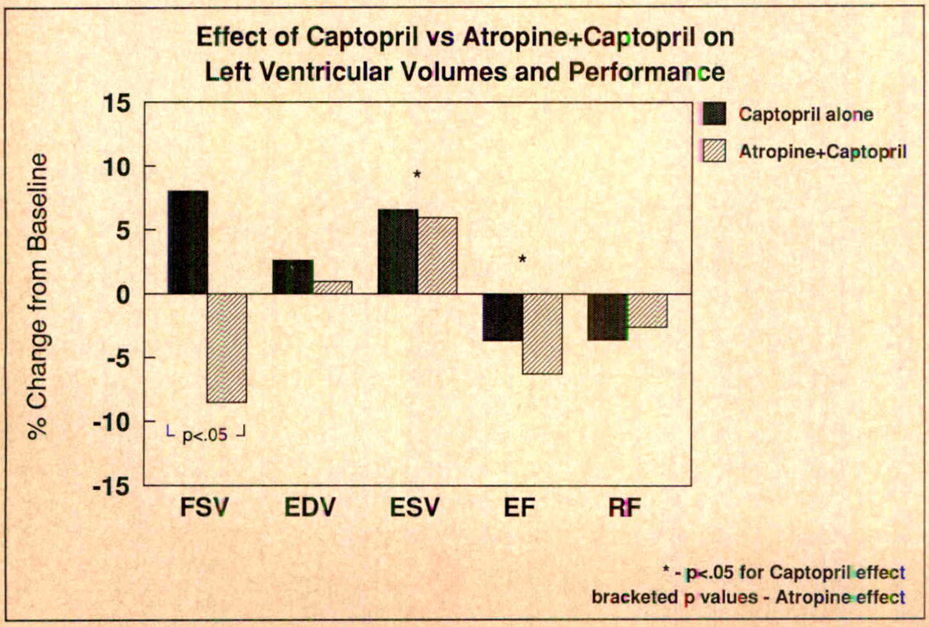

FIGURE 1. Percent changes from baseline produced by captopril alone or after pretreatment with atropine in forward stroke volume (FSV = cardiac output/heart rate), end-diastolic and end-systolic volumes (EDV and ESV), ejection fraction (EF) and regurgitant fraction (RF). *Asterisks* indicate that captopril had effect on measured parameter, and *bracketed* p value indicates significant difference in captopril response produced by atropine pretreatment between the 2 groups.

baseline produced by captopril for groups 1 and 2 are shown in Figure 1.

Pressure-volume loops consistently showed a lower systolic pressure over the range of systolic volumes (Figure 2) with no decrease in end-systolic volume despite decreased end-systolic pressure, which indicates a decline in inotropic state. This was measured as a significant decrease in the end-systolic pressure/volume quotient (Table I) and was corroborated by downward shifts in the preload-corrected ejection fraction-afterload relation (Figure 3).

Because the depressant effect of captopril on LV function may be parasympathetically mediated,[12,13] the above measurements were repeated after pretreatment with atropine in group 2 patients. However, by 2-way analysis of variance there was no difference between groups 1 and 2 in the response to captopril for regurgitant fraction, end-diastolic and end-systolic volumes, ejection fraction or end-systolic pressure/volume quotient. In contrast, the response of systemic resistance to captopril differed significantly between the 2 groups. As shown in Figure 3, evidence for a negative effect of captopril on a relatively load-independent index of ventricular performance was not abolished by atropine.

The possibility that radiographic contrast from the first LV cineangiography may affect the repeat measurements was assessed in an untreated control group (n = 5). There were no significant changes in heart rate (84 ± 13 to 83 ± 13 beats/min), mean arterial pressure (90 ± 10 to 89 ± 9 mm Hg), pulmonary wedge pressure (15 ± 6 to 14 ± 6 mm Hg), cardiac output (3.9 ± 1.0 to 3.6 ± 1.0 liters/min), end-diastolic volume (260 ± 64 to 262 ± 43 ml), end-systolic volume (117 ± 32 to 118 ± 35 ml), ejection fraction (0.55 ± 0.06 to 0.55 ± 0.07), regurgitant fraction (0.63 ± 0.15 to 0.66 ± 0.13) or end-systolic pressure/volume quotient (0.93 ± 0.25 to 0.78 ± 0.44 mm Hg/ml).

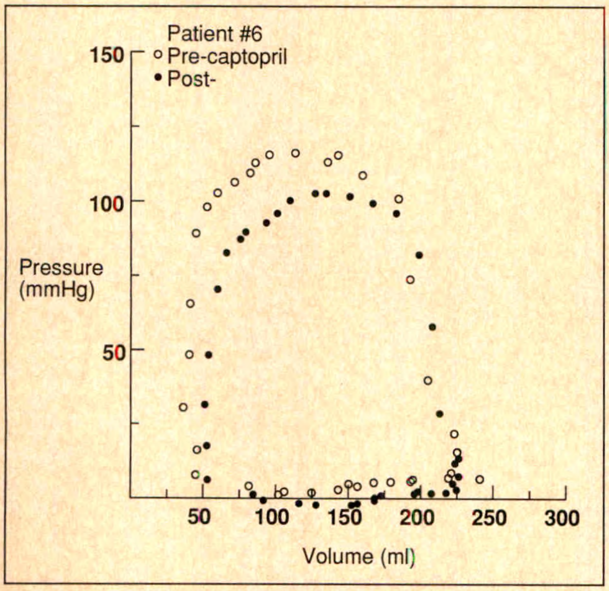

FIGURE 2. Micromanometer pressure and angiographic volume plotted frame-by-frame before (Pre-) and after (Post-) administration of captopril in patient with mitral regurgitation (group 1). End-systolic pressure volume ratio is measured from the pressure and volume of frame at *upper left shoulder of loop.*

DISCUSSION

The data indicate that in patients with chronic, severe MR, the short-term hemodynamic effects of captopril are not altogether favorable; although filling pressure decreases, captopril has a negative inotropic effect that blunts the anticipated effect of "unloading" on end-systolic volume, ejection fraction and regurgitant fraction.

Previous studies: The reported effects of angiotensin-converting enzyme inhibitors on cardiac output have often been quite modest. Packer et al[8] observed an im-

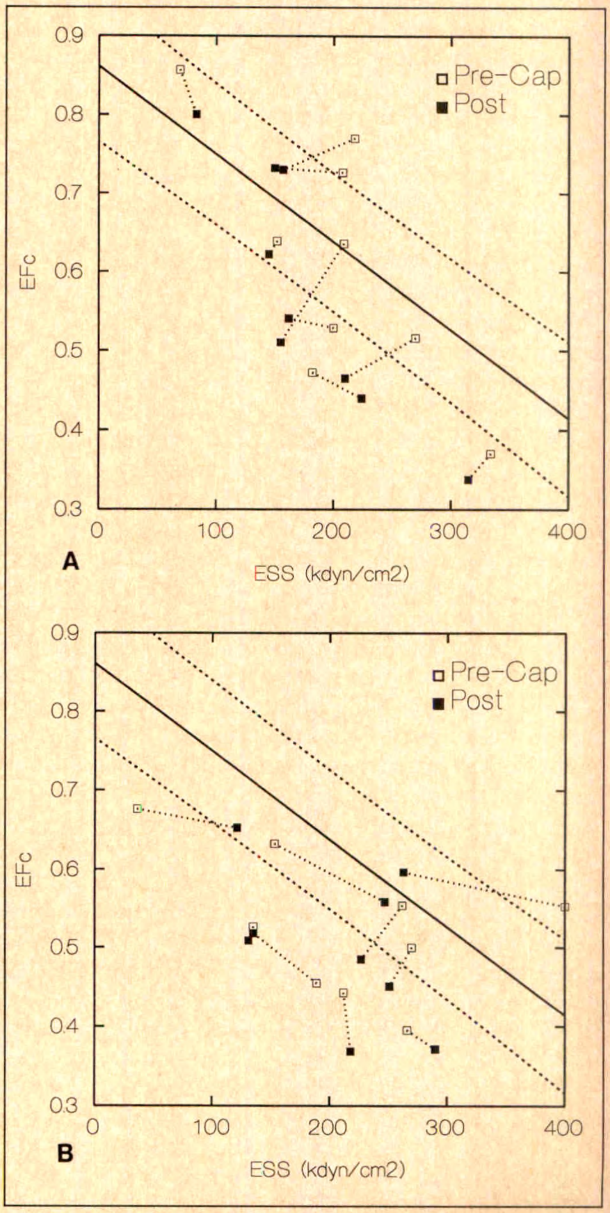

FIGURE 3. Relation of preload-corrected ejection fraction (EFc) to end-systolic stress (ESS) before (Pre) and after (Post) captopril (Cap) for patients in group 1 treated with captopril alone *(A)* and for patients in group 2 pretreated with atropine before captopril *(B)*. Ninety-five percent confidence limits for control group are indicated by *broken lines.*

mediate increase in cardiac index from 1.7 to only 1.9 liters/min/m^2 after administration of 30 mg of enalapril, with no further increase over time; a slightly greater and more sustained improvement over time was observed with captopril. In an earlier study,[1] the same investigators found that nitroprusside, administered in doses that reduced systemic resistance by the same amount as 25 mg of oral captopril, produced a two-fold greater increase in cardiac index than did captopril. Rouleau et al[2] had similar observations regarding captopril compared with prazosin and hydralazine (i.e., less increase in cardiac output for a given decrease in systemic resistance). Some of the difference may be due to differences in heart rate response to the different vasodilators. However, Dickstein[15] and Agostoni et al[16] also observed that cardiac output did not increase with short-term angiotensin-converting enzyme inhibitor therapy given to patients with heart failure, even though heart rate did not significantly decrease. Thus, for reasons that until now have not been stated, vasodilation with angiotensin-converting enzyme inhibitors may not produce the anticipated increase in systolic performance.

Loading conditions: The inability of systolic performance to improve after administration of captopril, despite a decrease in end-systolic pressure, could be due to a decrease in preload or inotropic state. In our patients, captopril reduced LV end-diastolic pressure, but not end-diastolic volume, suggesting no major preload reduction as would be expected with a venodilating effect. Thus, decreased preload does not appear to explain the inability of captopril to augment forward stroke volume in our patients.

Inotropic state: The alternative explanation for the failure of stroke volume to increase despite a decrease in afterload is that inotropic state decreased. Recently, Foult et al[3] found that intracoronary enalaprilat reduced measures of LV contractility. Our observation that end-systolic volume did not decrease (and actually slightly increased) despite a decrease in end-systolic pressure is also indicative of a negative inotropic effect. This was measured as a reduction in the end-systolic pressure/volume quotient in each patient and is illustrated by the pressure-volume loop shown in Figure 2. Although the end-systolic pressure/volume quotient is load-dependent, only if there were a decrease in end-systolic volume would the conclusion about inotropy be confounded by the load change. Furthermore, evidence for a negative inotropic effect is also demonstrated (Figure 3) using an index that is relatively independent of load.

There are several possible explanations for the negative inotropic effect observed after captopril therapy in this study: (1) a negative Treppe effect due to slowing of the heart rate; however, this phenomenon, which has been observed in isolated muscle, was found to be of minor importance in the clinical study of Higgins et al[17]; (2) by decreasing basal circulating or myocardial angiotensin II levels, angiotensin-converting enzyme inhibition removes positive inotropic stimulation by angiotensin II[18-21]; and (3) captopril may reduce myocardial performance by activating the parasympathetic nervous system. As discussed by Berne and Levy,[7] vagal stimulation (or acetylcholine infusion) may directly blunt contractility (possibly mediated by increased intracellular cyclic guanosine monophosphate) or may do so by inhibiting the sympathetic nervous system.

We examined the third postulate (that some of the inotropic effects of captopril may be mediated by the parasympathetic nervous system) and found that pretreatment with atropine did not enhance ejection fraction after administration of captopril and did not blunt the decline in either the end-systolic pressure/volume quotient or the ejection fraction-afterload relation produced by captopril. Thus, we believe the most likely mechanism for the negative inotropic effect is that angiotensin-converting enzyme inhibition removes the positive inotropic influence of angiotensin II.

A recent preliminary report[4] suggested that angiotensin-converting enzyme inhibitors may have disparate effects on myocardial function: depression of inotropic state, but improvement in lusitropic state (i.e., rate of relaxation). This may explain why filling pressures declined, with no decrease (or a slight increase) in filling volume.

Study limitations: This study, which was designed to examine the short-term effects of captopril by invasive methods, does not preclude a beneficial long-term effect of captopril on patients with MR. Another study limitation is in our clinical estimation of inotropic state, which at the present time is probably not possible to do with confidence with these or any other indexes.

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Comparison of Results of Percutaneous Mitral Valvuloplasty in Patients with Large (>6 cm) Versus Those with Smaller Left Atria

Fernando Alfonso, MD, Carlos Macaya, MD, Andrés Iñiguez, MD, Camino Bañuelos, MD,
Rosa Hernandez, MD, Javier Goicolea, MD, Antonio Fernandez-Ortiz, MD,
José Zamorano, MD, and Pedro Zarco, MD

To determine whether the presence of an aneurysmatic (severely enlarged) left atrium (>60 mm on echocardiography) influences results of percutaneous mitral valvuloplasty (PMV), the clinical, echocardiographic and hemodynamic characteristics and the results of this technique were compared in 46 consecutive patients with aneurysmatic left atrium (group I) and 125 consecutive patients without such echocardiographic finding (group II). Left atrial size was 70.5 ± 8 vs 50.1 ± 6 mm ($p < 0.005$) in groups I and II, respectively. Patients in group I were older (57 ± 12 vs 48 ± 12 years, $p < 0.025$), more symptomatic (New York Heart Association functional class ≥III or IV: 67 vs 42%, $p < 0.05$), and had atrial fibrillation more frequently (91 vs 44%, $p < 0.001$). The echocardiographic score (8.9 ± 1.9 vs 7.5 ± 2, $p < 0.005$) and the incidence of mild mitral regurgitation on angiography before PMV (54 vs 30%, $p < 0.01$) was also higher in group I patients. Hemodynamic parameters before PMV were similar in both groups, but after the procedure, final mitral valve area (1.61 ± 0.5 vs 1.95 ± 0.4 cm^2, $p < 0.05$) and the absolute increase in mitral area (0.81 ± 0.3 vs 1.02 ± 0.3 cm^2, $p < 0.05$) were lower and mean pulmonary artery pressure (35 ± 10 vs 28 ± 9 mm Hg, $p < 0.025$) was higher in group I. More difficulties in crossing the interatrial septum (9 vs 0%, $p < 0.01$) were also found in group I. PMV success (mitral valve area increase ≥50% without complications) tended to be lower (83 vs 94%, $p < 0.1$) and dilatation failure higher (11 vs 1%, $p < 0.01$) in group I, but the incidence of major complications was similar in both groups. An optimal result (final mitral valve area ≥1.5 cm^2) was found more frequently (88 vs 61%, $p < 0.05$) in group II patients. In addition, on multivariate analysis, an aneurysmatic left atrium was an independent predictor of PMV suboptimal results.

In conclusion, patients with mitral stenosis and aneurysmatic left atrium may successfully undergo PMV, but they have more severe mitral valve disease and experience technically difficult procedures, dilatation failure and suboptimal results more often than patients with smaller left atria.

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Surgical mitral commissurotomy is an effective and time-honored treatment for selected patients with mitral stenosis.[1-3] More recently, percutaneous mitral valvuloplasty (PMV) has emerged as an attractive therapeutic alternative for patients with mitral stenosis and adequate mitral valves providing optimistic short and mid-term results.[4-6] Candidates for surgical commissurotomy are generally also suitable for PMV. However, patients with mitral stenosis who have more than mild mitral regurgitation are usually not considered for PMV. In addition, PMV involves catheter manipulation within the left atrium; therefore, the technique is not indicated in patients who present with left atrial thrombus on 2-dimensional echocardiography.[6,7] On the other hand, different studies[8,9] have suggested that some anatomic features of the mitral valve may influence the outcome of the procedure and should be used in the decision-making process involved in the selection of patients for this technique. Nevertheless, the potential influence of other factors, such as left atrial size, on the results of PMV have not been established. Accordingly, the present investigation was undertaken to determine the role that the presence of a severely enlarged left atrium plays on the results of this technique in a consecutive series of patients.

METHODS

Patients: From February 1989 to January 1991, 171 consecutive patients underwent PMV in our institution. Each patient had a history of rheumatic mitral valve disease with physical signs of moderate or severe mitral stenosis. Inclusion criteria for PMV included mitral stenosis with mitral valve area <1.5 cm^2 and New York Heart Association functional class ≥II. Patients with echocardiographic evidence of a left atrial thrombus and those with more than mild mitral regurgitation were excluded. Mean age of the group was 51 ± 11 years and 34 patients (20%) were men. All patients were symptomatic, 84 (49%) were in New York Heart Association functional class ≥III, 97 (57%) had atrial fibrillation, 32 (19%) had a previous history of pulmonary edema, and 37 patients (22%) had previously experienced a systemic emboli. Only patients with an elapsed time from the embolic event >3 months were

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included. Before PMV, 6 patients had refused cardiac surgery and 17 were considered at high surgical risk. Patients were classified into 2 groups on the basis of left atrial size: 46 patients (27%) had aneurysmatic (severely enlarged) left atria (group I) and 125 patients (73%) had smaller left atrial sizes (group II).

Echocardiographic protocol: All patients underwent a complete 2-dimensional echocardiographic examination including pulsed, continuous, and color Doppler echocardiography before and after PMV. Measurements were obtained according to the recommendations of the American Society of Echocardiography.[10,11] Special care was taken to identify accurately the posterior wall of the left atrium from M-mode recordings guided by 2-dimensional echocardiography, and patients with a left atrial size >60 mm were considered to have aneurysmatic left atrium. A complete examination of the left atrium was performed to rule out left atrial thrombi. Features of the mitral valve and subvalvular apparatus were analyzed from different views and the Wilkins score was calculated.[8] Mitral valve area was determined from the pressure half-time method after analyzing ≥3 beats.[12] In addition, the appearance of the commissures was studied in detail from the parasternal short-axis view at the mitral valve level. Mitral regurgitation was graded (I to III) with color Doppler as suggested by Helmcke et al[13] and patients with mitral regurgitation ≥II/III on color Doppler were not considered candidates for PMV.

Valvuloplasty procedure: All patients underwent right and left hemodynamic measurements from the left groin with determination of mitral valve gradient and cardiac output (thermodilution technique) before and after PMV. A left ventricular angiography (30° right anterior oblique projection) was also performed before and after the procedure to detect the presence and severity of mitral regurgitation. Mitral valve area was calculated by the Gorlin formula[14] and mitral regurgitation was graded I to III. PMV procedures were performed from the right femoral vein with the Inoue monoballoon technique in 133 patients (78%) and with the double balloon technique in the remaining 38 (22%). A bolus dose of intravenous heparin (100 U/kg) was administered in every patient after the transeptal puncture.

PMV with the Inoue catheter was performed according to a previously described technique.[4] In brief, after a standard transeptal puncture was performed, a guidewire was advanced through the transeptal catheter to be coiled into the left atrium. The balloon catheter with its stiffened tip was then advanced to the left atrium. Subsequently, a change in the catheter tip configuration to its flexible position permitted its complete introduction into the left atrium. Finally, with appropriate catheter manipulation, the balloon was gently pushed across the mitral valve. Care was taken to pass the partially inflated balloon through the mitral orifice avoiding transchordal passage. At this time a progressive stepwise inflation of the balloon allowed first its stabilization and second the dilatation of the mitral valve.

The double balloon technique was performed in 16 patients using a single double balloon catheter, and in the remaining 22 patients with 2 separate balloons.[15] After the transeptal puncture was performed the interatrial septum was dilated with a 6 mm balloon catheter. In patients in whom the double balloon technique was used, both balloons were introduced by the same venous and transeptal puncture. Various inflations were then performed until the indentation of the balloons caused by the mitral valve was no longer seen. Balloon diameters were selected according to body surface area. Balloon-effective dilating areas were calculated assuming a circular area for monoballoons and using a previously described formula for double balloons.[16] Thus, balloon diameters in the monoballoon technique were 26, 28 and 30 mm for body surface areas of <1.5, 1.5 to 1.7 and >1.7 m^2, whereas in the double balloon technique balloon diameters were 18 × 18, 18 × 20 and 20 × 20 mm for body surface areas of <1.5, 1.5 to 1.7 and > 1.7 m^2, respectively.

Definitions: Dilatation success was defined as a gain in mitral valve area ≥50%. PMV success was considered when dilatation success was obtained in the absence of complications. In patients with dilatation success, optimal results were considered if final mitral valve area was ≥1.5 cm^2.

Statistical analysis: Different clinical, echocardiographic, hemodynamic and angiographic data were prospectively collected on a standardized form and subsequently introduced into a database specifically designed for PMV (Valvulosystem™, Seattle software, Seattle, Washington, and Cormedica, Barcelona). The chi-square test (with the Yate's correction when appropriate) was used to determine differences in categorical variables. The unpaired Student's *t* test was used to compare continuous variables which are presented as mean ± SD. A p value of <0.05 was considered statistically significant. A stepwise logistic regression analysis (SPSS PC + 3.1, Microsoft Corporation) was used to identify variables independently associated to an aneurysmatic left atrium, to PMV success and to PMV suboptimal results. Our definition of PMV optimal results (final mitral area ≥1.5 cm^2) is strongly dependent on the absolute value of mitral valve area before dilation; thus, the analysis of factors related to PMV suboptimal results was also repeated after excluding this variable.

RESULTS

Baseline clinical characteristics of both groups are listed in Table I. Group I patients were older, more symptomatic (New York Heart Association functional class ≥III, 31 [67%] vs 53 [42%], p <0.05), and had more frequently atrial fibrillation and a previous history of congestive heart failure. Patients in this group were also more frequently treated with digoxin and coumadin. The cardiothoracic ratio on the chest x-ray film was higher in group I patients (0.62 ± 0.09 vs 0.52 ± 0.05, p <0.005). Echocardiographic findings in groups I and II are presented in Table II. Patients in group I had larger left ventricles and mitral anular size. The echocardiographic score of this group of patients was higher, mainly as the result of thicker valves with more severe subvalvular disease. Hemodynamic features in both groups of patients are summarized in Table III.

TABLE I Clinical Characteristics

	Group I (46)	Group II (125)	p Value
Age (years)	57 ± 12	48 ± 12	<0.025
Women	37 (80%)	100 (80%)	NS
NYHA II	15 (32%)	72 (58%)	<0.01
NYHA III	27 (59%)	49 (39%)	<0.05
NYHA IV	4 (9%)	4 (3%)	NS
Atrial fibrillation	42 (91%)	55 (44%)	<0.001
Previous history			
Right-sided CHF	10 (22%)	5 (4%)	<0.001
Pulmonary edema	11 (24%)	21 (17%)	NS
Surgical commissurotomy	9 (19%)	14 (11%)	NS
Systemic emboli	14 (30%)	23 (18%)	NS
Treatment			
Digoxin	45 (98%)	86 (69%)	<0.001
Diuretics	41 (91%)	100 (80.0%)	NS
Coumadin	38 (83%)	60 (48%)	<0.001

CHF = congestive heart failure; NS = not significant; NYHA = New York Heart Association functional class.

TABLE II Echocardiographic Features Before Valvuloplasty

	Group I	Group II	p Value
Measurements			
Left atrium (mm)	70.5 ± 8	50.1 ± 6	<0.005
Left ventricle (diastole) (mm)	49.4 ± 8	45.5 ± 6	<0.05
Left ventricle (systole) (mm)	31.1 ± 7	28.2 ± 5	NS
Mitral anulus (mm)	41.8 ± 5	36.7 ± 4	<0.025
Total score	8.9 ± 1.9	7.5 ± 1.7	<0.01
Calcification (I–IV)	2.1 ± 0.9	1.6 ± 0.8	NS
Thickening (I–IV)	2.6 ± 0.6	2.2 ± 0.6	<0.05
Subvalvular involvement (I–IV)	2.5 ± 0.7	2.0 ± 0.6	<0.025
Flexibility (I–VI)	1.8 ± 0.7	1.7 ± 0.6	NS

NS = not significant.

TABLE III Hemodynamic and Angiographic Findings Before Valvuloplasty

	Group I	Group II	p Value
Mitral valve gradient (mm Hg)	13.9 ± 5	14.9 ± 6	NS
Cardiac index (liters/m/m^2)	2.2 ± 0.4	2.4 ± 0.6	NS
Mitral valve area (cm^2)	0.83 ± 0.2	0.94 ± 0.2	NS
Systolic pulmonary artery pressure (mm Hg)	57.3 ± 14	50.6 ± 19	NS
Mean pulmonary artery pressure (mm Hg)	39.0 ± 10	34.9 ± 12	NS
Mean left atrial pressure (mm Hg)	29.1 ± 7	25.0 ± 8	NS
Left ventricular ejection fraction (%)	60.3 ± 7	63.7 ± 7	NS
Mild mitral regurgitation	25 (54%)	37 (30%)	<0.01

*p < 0.1.
NS = not significant.

The presence of mild (I/III) mitral regurgitation was significantly higher in group I patients. In addition, on multivariate analysis, the presence of atrial fibrillation (p <0.001), subvalvular involvement (p <0.001), mitral valve thickening (p <0.05) and mild mitral regurgitation (p <0.05) were pre-PMV variables independently associated with patients with an aneurysmatic left atrium.

The technique of PMV used was similar in both groups (Inoue monoballoon in 39 [85%] and 93 [75%], p = not significant [NS], and the double balloon technique in 7 [15%] and 32 [25%] [p = NS] patients in groups I and II, respectively). The duration of the procedure was slightly longer (95 ± 30 vs 87 ± 26 minutes) in group I patients, but far from reaching significant value, and, more technical difficulties were also found in this group during transeptal puncture (4 [9%] vs 0 [0%], p <0.01), and in crossing the mitral valve (3 [7%] and 6 [5%], p = NS).

PMV was considered a successful procedure more often in group II patients (117 [94%] vs 38 [83%], p <0.1), and more patients in group I had dilatation failure without complications (5 [11%] vs 1 [1%], p < 0.01). In patients with PMV success, optimal results were found more frequently among patients without an aneurysmatic left atrium (103 [88%] vs 23 [61%], p <0.05). In addition, left atrial size was significantly higher in patients with suboptimal PMV results (60 ± 14 vs 53 ± 9 mm, p <0.005). The hemodynamic findings after PMV are listed in Table IV. After PMV, mi-

TABLE IV Hemodynamic and Angiographic Data After Valvuloplasty

	Group I	Group II	p Value
Mitral valve gradient (mm Hg)	5.5 ± 2.8	4.8 ± 2.4	NS
Cardiac index (liters/m/m^2)	2.4 ± 0.6	2.7 ± 0.6	NS
Mitral valve area (cm^2)	1.61 ± 0.5	1.95 ± 0.4	<0.025
Systolic pulmonary artery pressure (mm Hg)	51.4 ± 13	41.6 ± 13	<0.025
Mean pulmonary artery pressure (mm Hg)	35.0 ± 9	28.3 ± 9	<0.025
Mean left atrial pressure (mm Hg)	21.7 ± 6	16.3 ± 6	<0.01
Left ventricular ejection fraction (%)	56.2 ± 8	59.8 ± 7	NS
Mitral regurgitation			
Mild (I/III)	30 (65%)	54 (44%)	<0.025
Moderate (II/II)	8 (18%)	17 (13%)	NS
Severe (III/II)	2 (4%)	6 (5%)	NS

NS = not significant.

tral valve areas were significantly smaller and the absolute increase in mitral valve area was also smaller in group I patients (0.81 ± 0.3 vs 1.02 ± 0.3 cm^2, $p < 0.05$). In addition, after PMV, pulmonary artery pressures and mean left atrial pressures remained significantly higher in group I. The number of patients with partial (7 vs 4%) or complete (38 vs 26%) splitting of only 1 commissure and the number of patients with complete splitting of 1 commissure and partial (25 vs 32%) or complete splitting of the other (19 vs 32%), as determined in the echocardiographic study immediately after PMV, was similar in groups I and II, respectively. Procedural complications including cardiac tamponade (2 [4%] vs 1 [1%], p = NS), severe mitral regurgitation (2 [4%] vs 6 [5%], p = NS), and the need for surgical vascular repair (1 [2%] vs 0 [0%], p = NS) were also similar in groups I and II. One patient in each group required emergency cardiac surgery (1 patient for cardiac tamponade and the other for acute severe mitral regurgitation) and 1 patient in group II required elective surgery for severe mitral regurgitation before discharge. No other complications were observed and no death was related to the procedure. After successful PMV, most patients experienced symptomatic improvement (New York Heart Association functional class improvement ≥1 grade): 94 and 93% in groups I and II, respectively. The results of PMV in the 2 groups were not related to the technique used (monoballoon versus double balloon).

Finally, to determine if an aneurysmatic left atrium was independently related to either dilatation failure or PMV suboptimal result, different variables were entered in a stepwise logistic regression analysis. None of the analyzed variables was independently associated to PMV failure. On univariate analysis, age, New York Association functional class, atrial fibrillation, echocardiographic score, left atrial size >60 mm, mitral valve area before PMV, cardiac index and systolic pulmonary artery pressure, were variables associated with PMV suboptimal results. However, on multivariate analysis only a low mitral valve area before PMV ($p = 0.001$) and a left atrial size >60 mm ($p = 0.03$) were independent predictors of PMV suboptimal results. When mitral valve area before PMV was excluded from the analysis, the echocardiographic score ($p = 0.009$), a left atrial size >60 mm ($p = 0.01$) and a reduced cardiac index ($p = 0.03$) appeared as independent predictors of PMV suboptimal results.

DISCUSSION

PMV is a new and expanding therapeutic technique for treating selected patients with symptomatic mitral stenosis.[4,5] The clinical, echocardiographic and angiographic profile of patients in whom optimal PMV results should be expected is currently under investigation, but major guidelines have already been established.[5,6] Young patients in sinus rhythm, with a good quality opening snap and no history of a recent embolic event, are considered good candidates from the clinical point of view.[5,6] Two-dimensional echocardiography allows an accurate examination of the anatomic characteristics of the mitral valve, so that the degree of calcification, thickening, mobility and subvalvular involvement can be readily ascertained. Wilkins et al[8] suggested that all these 4 echocardiographic parameters may be used to estimate a global echocardiographic score that should be used to identify patients with suitable mitral valves for PMV. However, most studies have been unable to identify the subgroup of patients at higher risk for procedural-related complications.[17,18] This may be partly related to the fact that PMV complications are rare and have different etiologies (embolism, tamponade, severe mitral regurgitation), as occurred in the present study. Therefore, it appears that preprocedural markers of successful PMV outcome are still required.

Results of mitral valvuloplasty in patients with aneurysmatic left atrium: No information exists concerning the possible influence of a severely enlarged left atrium on the results of PMV. From observations in our initial experience with the procedure we hypothesized that patients with mitral stenosis and aneurysmatic left atria could have more cumbersome procedures. The results of the present study demonstrate that patients with mitral stenosis and aneurysmatic left atria have some peculiarities with regard to PMV. First, they have more severe mitral valve disease and clinically they are older, more symptomatic and frequently have atrial fibrillation. Second, they have a higher echocardiographic score mainly as the result of thicker mitral valves with more severe subvalvular involvement. They also have larger left ventricles and a higher incidence of mild mitral regurgitation. Third, they frequently present with difficulties in crossing the interatrial septum, and they also have a higher rate of dilatation failure. In addition, despite similar baseline hemodynamic characteristics, patients with aneurysmatic left atria have smaller mitral valve areas and a lower reduction in pulmonary artery pressure after PMV than other patients.

The reason for the poorer PMV results of patients with aneurysmatic left atrium is unknown. However, one could speculate that different factors may predispose either to technically difficult procedures leading to dilatation failure or, alternatively, to PMV suboptimal results. The altered anatomy of patients with aneurysmatic left atrium may increase the likelihood of technical difficulties during the procedure, as occurred in the present series. When the left atrium becomes severely enlarged the normal relation of the interatrial septum with the adjacent anatomic structures may experience a significant change. This may modify the angle required for the transeptal puncture, and may induce a puncture in the interatrial septum in a site different from the fossa ovalis that, in turn, will provide an unusual (and less favorable) relation with the mitral valve orifice. In addition, all these factors may increase the difficulties encountered in crossing the mitral valve and in obtaining an optimal positioning of the balloon across the valve at the time of inflation. Sheikh et al[19] described that the presence of marked atrial septal thickening could prevent performing the procedure by the anterograde approach. None of the patients in this series had such echocardiographic finding, so our difficulties in crossing the interatrial septum are unlikely due to this factor. The association of aneurysmatic left atrium to patients with more severe mitral valve disease may also induce poorer PMV results. In fact, we also found that the presence of a high echocardiographic score was independently associated to PMV suboptimal results. However, despite the adverse baseline characteristics of patients with aneurysmatic left atrium, the present investigation demonstrates that the presence of an aneurysmatic left atrium is an independent predictor of PMV suboptimal results. In a recent study, Hung et al[20] found that left atrial size was significantly higher (55 vs 49 mm) in patients with a mitral valve area gain $<$ 50% after PMV, but in that study, left atrial size was not predictive of poorer PMV results on multivariate analysis.

The presence of an aneurysmatic left atrium may enhance the likelihood of left atrial thrombus, but no patient in this series had an echocardiographic image suggestive of left atrial clot, and this may explain the absence of embolic complications in the present study. Although it seems attractive to suggest the systematic use of transesophageal echocardiography before PMV in this cohort of patients to rule out the possibility of a left atrial appendage thrombus, no conclusive data support this strategy. In addition, although patients with aneurysmatic left atrium more often have mild mitral regurgitation before PMV, the development of moderate or severe mitral regurgitation after PMV in this series was similar in both groups. This is in accordance with previous studies[21,22] and with the recent report by Sancho et al,[23] which demonstrated that although left atrial size was related to the appearance of mitral regurgitation after PMV on univariate analysis, this association disappeared on multivariate analysis. Furthermore, as in our study, progression of mitral regurgitation could not be predicted by the presence of mild mitral regurgitation before PMV. Finally, in our series, the results of PMV in patients with aneurysmatic left atrium were not related to the technique used (mono- versus double balloon), supporting the results reported by other investigators[24,25] and our previous experience in the general population of patients undergoing PMV.[26]

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Hemodynamic Effects of Nitroprusside on Valvular Aortic Stenosis

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The effects of acute reduction of left ventricular (LV) loading in valvular aortic stenosis (AS) were examined. Thirty-five consecutive patients with AS (peak-to-peak aortic valve gradient 66 ± 26 mm Hg, aortic valve area 0.65 ± 0.22 cm^2) were given intravenous sodium nitroprusside (1 to 3 μg/kg/min) to reduce systolic aortic pressures by >10 mm Hg (mean aortic pressure 99 ± 15 to 80 ± 15 mm Hg; $p < 0.001$).

Overall, nitroprusside infusion resulted in little change in cardiac index (2.72 ± 0.61 to 2.67 ± 0.58 liters/min/m^2; p = not significant). Individual patients had a range of responses. Fourteen patients (group 1) had an increase in cardiac index (2.42 ± 0.59 to 2.74 ± 0.67 liters/min/m^2; $p < 0.001$), whereas 21 (group 2) had a decrease or no change (2.93 ± 0.56 to 2.61 ± 0.52 liters/min/m^2; $p < 0.001$). Comparison of these subgroups showed that a cardiac index increase with nitroprusside was significantly predicted by a higher LV end-diastolic pressure (26 ± 12 vs 15 ± 6 mm Hg), lower LV ejection fraction (44 ± 18 vs 62 ± 12%), smaller aortic valve area (0.52 ± 0.12 vs 0.74 ± 0.22 cm^2) and lower cardiac index (2.42 ± 0.59 vs 2.93 ± 0.56 liters/min/m^2) (all values groups 1 and 2, respectively).

It is concluded that there is a disparate response to acute vasodilatation in AS. Potentially beneficial effects are seen in a subgroup of patients, especially those with increased filling pressures and impaired LV function. It is postulated that the hemodynamic effects of sodium nitroprusside in patients with AS can be explained by the balance of effects on preload and afterload.

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Valvular aortic stenosis (AS) of any severity is generally regarded as a contraindication to vasodilator therapy. The reasons underlying this recommendation are based on the concept that the afterload is relatively fixed by the valvular obstruction and that vasodilatation would result in harmful hypotension. Published data on the harm or benefit of vasodilator therapy in AS is meager. The few available small studies suggest a beneficial effect of vasodilatation in some patients.[1–4] We studied the hemodynamic effects of short-term alteration of left ventricular (LV) loading with sodium nitroprusside in patients with isolated AS and a range of LV function in an attempt to identify those who may benefit from vasodilator therapy.

METHODS

Thirty-five consecutive patients (14 female and 21 male, mean age 65 years, range 16 to 83) undergoing routine diagnostic right- and left-sided heart catheterization for suspected pure AS were studied. Written informed consent was obtained before the procedure. Usual medication was withheld on the day of the study. Premedication with 10 mg of diazepam was given orally 1 hour before the procedure. Right-sided heart catheterization was performed through the right femoral vein using a 7Fr thermodilution Swan-Ganz catheter. Either femoral artery sheath or radial artery cannula was used to monitor systemic arterial pressure. A 7 or 8Fr pigtail catheter was positioned in the left ventricle by the retrograde aortic approach, using a separate catheter to cross the valve if necessary.[5] Pressures were recorded at end-expiration with the 0 reference at the midthoracic level, and thermodilution cardiac output was measured using room temperature injectate.[6] Control recordings of cardiac output (in triplicate), right atrial, peripheral arterial and LV pressures, and heart rate were obtained after 5 minutes of rest. Sodium nitroprusside (Nipride, Roche) was infused at a rate of 1 μg/kg/min (increased to 3 μg/kg/min, if necessary) to produce a decrease of 10 mm Hg in systolic aortic pressure, the infusion was continued for 5 minutes, and recordings were repeated. Routine catheterization was then completed.

Central aortic and peripheral arterial pressure traces were compared, and any significant difference in pressure was allowed for in gradient calculation. Peak-to-peak aortic valve gradient was then calculated by time alignment of peripheral arterial and LV pressure tracings.[7] Aortic valve area was calculated by the modified Gorlin formula.[8] LV ejection fraction and volume were determined by averaging computerized planimetry of 3 beats of the cineventriculogram obtained in the 30-degree right anterior oblique projection. Systemic vascular

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TABLE I Individual Patient Data

		LV-SA PSG		AVA		LVEDP		CI		LVP		MAP		HR	
dCI	LVEF	Rest	NP	Rest	NP	Rest	NP	Rest	NP	Rest	NP	Rest	NP	Rest	NP
1.01	0.80	53	67	0.60	0.84	18	12	2.55	3.56	193	180	83	69	64	69
0.96	0.25	37	36	0.53	0.84	31	25	2.26	3.22	187	176	100	83	74	87
0.59	0.38	117	143	0.47	0.52	26	25	2.54	3.13	255	237	78	63	76	83
0.46	0.38	67	71	0.68	0.77	15	16	2.99	3.45	188	171	83	63	67	71
0.26	0.46	85	57	0.57	0.49	5	6	1.86	2.12	204	129	85	58	85	57
0.26	0.46	61	78	0.63	0.54	12	6	2.68	2.94	210	161	104	58	94	111
0.25	0.50	77	89	0.35	0.36	36	24	2.36	2.61	242	229	92	81	61	64
0.21	0.38	49	61	0.59	0.53	27	14	1.90	2.11	163	126	91	54	71	72
0.19	0.72	130	135	0.53	0.56	27	21	2.87	3.06	263	251	96	92	61	62
0.10	0.22	80	84	0.52	0.45	47	44	3.17	3.27	179	166	85	69	105	120
0.10	0.55	67	80	0.25	0.21	15	15	1.28	1.38	178	171	96	80	67	80
0.09	0.47	79	89	0.51	0.46	34	25	3.28	3.37	205	195	87	81	103	113
0.05	0.15	38	39	0.53	0.53	30	25	1.63	1.68	143	137	85	76	84	82
0.01	0.49	39	90	0.38	0.41	43	30	2.44	2.45	258	209	98	78	89	90
0	0.63	29	22	1.01	0.94	9	6	2.93	2.93	214	210	120	118	73	82
−0.01	0.70	54	48	0.74	0.83	14	9	2.80	2.79	231	203	130	110	77	86
−0.01	0.60	37	52	0.69	0.56	24	15	2.38	2.37	235	200	123	93	59	69
−0.03	0.60	40	63	1.08	0.78	11	13	3.01	2.98	228	182	129	80	105	109
−0.05	0.66	33	94	0.53	0.32	15	13	3.12	3.07	243	226	85	81	83	94
−0.08	0.61	46	43	0.76	0.74	18	9	2.98	2.90	185	150	94	75	67	75
−0.10	0.56	40	108	0.78	0.74	7	5	2.15	2.05	178	189	95	59	65	113
−0.12	0.47	131	136	0.48	0.43	17	10	2.59	2.47	254	239	87	73	63	68
−0.23	0.83	43	45	1.14	1.11	11	8	4.22	3.99	156	146	85	79	76	88
−0.23	0.77	43	59	0.78	0.60	23	17	2.23	2.00	235	206	124	96	61	61
−0.25	0.61	80	79	0.44	0.39	17	18	2.27	2.02	210	190	90	76	59	63
−0.28	0.67	70	64	0.71	0.58	16	8	2.78	2.50	218	199	98	98	67	61
−0.31	0.38	65	73	0.81	0.66	25	5	3.14	2.83	204	188	88	77	85	93
−0.34	0.65	53	70	0.68	0.52	16	8	2.40	2.06	238	185	122	95	66	67
−0.48	0.61	38	51	1.17	0.91	10	4	3.43	2.95	201	168	111	85	75	92
−0.52	0.39	101	98	0.42	0.34	10	5	2.47	1.95	235	210	101	85	81	92
−0.56	0.41	68	73	0.78	0.64	14	7	3.85	3.29	230	193	112	76	98	98
−0.57	0.67	73	65	0.46	0.49	4	5	2.72	2.15	187	172	91	65	103	84
−0.65	0.75	50	47	0.84	0.61	21	11	3.21	2.56	211	179	119	98	93	81
−0.68	0.80	65	75	0.65	0.51	10	4	3.12	2.44	215	195	108	94	82	86
−0.85	0.59	71	74	0.68	0.52	15	7	3.63	2.78	218	195	103	76	115	115

AVA = aortic valve area (cm^2); CI = cardiac index (liters/min/m^2); dCI = change in cardiac index with nitroprusside (liters/min/m^2); HR = heart rate (beats/min); LV = left ventricular; LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEF = left ventricular ejection fraction; LVP = left ventricular systolic pressure (mm Hg); MAP = mean arterial pressure (mm Hg); NP = during nitroprusside infusion; PSG = peak systolic gradient (mm Hg); Rest = at rest before nitroprusside; SA = systemic artery.

resistance and LV stroke work indexes were calculated according to standard formulas.[9,10] We considered the afterload to consist of 2 components (Figure 1). The contribution to afterload at the level of the aortic valve (valvular afterload) was calculated as the pressure decrease across the valve/cardiac index. At the periphery, vascular afterload was considered to be equal to the systemic vascular resistance index.

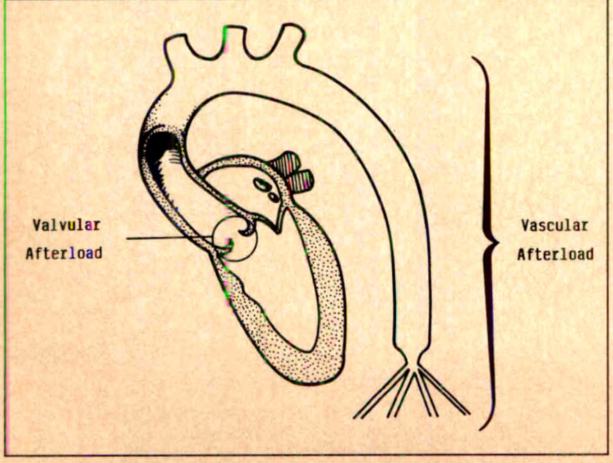

FIGURE 1. Diagramatic representation of sites of valvular and vascular afterload in patients with aortic stenosis.

Data are presented as mean ± standard deviation in the text and Tables, and mean ± standard error of the mean in the Figures. Data were compared using Student's paired or independent sample *t* tests, as appropriate. Two-tailed probabilities were determined from published tables, and statistical significance was assumed at the $p < 0.05$ level.

RESULTS

Patients tolerated the study well, without adverse events, and complete data was obtained in all cases. Individual patient data are listed in Table I, and mean data are listed in Table II. Nitroprusside infusion resulted in a decrease in mean arterial pressure (99 ± 15 to 80 ± 15 mm Hg; $p < 0.001$) and systemic vascular resistance index (2,896 ± 796 to 2,347 ± 719 dynes · s · cm^{-5}/m^2; $p < 0.001$). Overall, cardiac index did not change significantly (2.72 ± 0.61 to 2.67 ± 0.58 liters/min/m^2). Calculated aortic valve area decreased (0.65 ± 0.22 to 0.59 ± 0.20 cm^2; $p < 0.001$) and peak aortic valve gradient increased (66 ± 26 to 73 ± 28 mm Hg;

TABLE II Cardiac Index Response to Nitroprusside Infusion (all patients, n = 35)

	Control	During Nitroprusside	p Value
Cardiac index (liters/min/m^2)	2.72 ± 0.61	2.67 ± 0.58	NS
Left ventricular end-diastolic pressure (mm Hg)	19 ± 10	14 ± 9	<0.001
Systemic vascular resistance index (dynes · s · cm^{-5}/m^2)	2,896 ± 796	2,347 ± 719	<0.001
Mean arterial pressure (mm Hg)	99 ± 15	80 ± 15	<0.001
Calculated aortic valve area (cm^2)	0.65 ± 0.22	0.59 ± 0.20	<0.001
Left ventricular–systemic artery peak systolic gradient (mm Hg)	66 ± 0.26	73 ± 28	<0.05
Heart rate (beats/min)	78 ± 15	84 ± 17	<0.001

NS = not significant.

TABLE III Cardiac Index Response to Nitroprusside Infusion

	Group 1 (cardiac index up)— 14 Patients	Group 2 (cardiac index down)— 21 Patients	p Value
Aortic valve area (cm^2)	0.52 ± 0.12	0.74 ± 0.22	<0.01
Left ventricular-systemic artery peak systolic gradient (mm Hg)	74 ± 27	61 ± 24	NS
Left ventricular ejection fraction (%)	44 ± 18	62 ± 12	<0.01
Left ventricular end-systolic volume (ml)	81 ± 48	47 ± 25	<0.05
Left ventricular end-diastolic pressure (mm Hg)	26 ± 12	15 ± 6	<0.01
Cardiac index (liters/min/m^2)	2.42 ± 0.59	2.93 ± 0.56	<0.05
Left ventricular stroke work index (g · m · m^2)	80 ± 32	102 ± 13	<0.05
Mean systemic arterial pressure (mm Hg)	90 ± 8	105 ± 16	<0.05
Systemic vascular resistance index (dynes · s · cm^{-5}/m^2)	2,977 ± 880	2,829 ± 738	NS

NS = not significant.

p <0.01). Heart rate also increased significantly (78 ± 15 to 84 ± 17 beats/min; p <0.001). LV end-diastolic pressure decreased significantly (19 ± 10 to 14 ± 9 mm Hg; p <0.001) with nitroprusside infusion.

The patients were grouped according to their cardiac index responses to nitroprusside. Fourteen patients (group 1) exhibited an increase in cardiac index (2.42 ± 0.59 to 2.74 ± 0.67 liters/min/m^2; p <0.001), and 21 (group 2) a decrease (2.93 ± 0.56 to 2.61 ± 0.52 liters/min/m^2; p <0.001). There were significant differences between the characteristics of these 2 groups (Table III). Other variables, both demographic and hemodynamic, were not significantly different. The group responding with an increase in cardiac index to nitroprusside (group 1) were identified by poorer LV systolic function, higher preload and more severe AS. Responses to changes in preload (LV end-diastolic pressure) and vascular afterload (systemic vascular resistance index) caused by nitroprusside are presented in Figures 2 to 5. Initial LV end-diastolic pressure was significantly higher in group 1 than in 2 (26 ± 12 vs 15 ± 6 mm Hg; p <0.01), whereas systemic vascular resistance index was similarily high in both groups (2,977 ± 880 vs 2,829 ± 738 dynes · s · cm^{-5}/m^2, groups 1 and 2, respectively; p = not significant). LV end-diastolic pressure decreased with nitroprusside, but remained above normal in group 1 (26 ± 12 to 20 ± 10 mm Hg; p <0.001), whereas it decreased from lower initial levels in group 2 (15 ± 6 to 9 ± 4 mm Hg; p <0.001). In group 1, systemic vascular resistance index decreased to within the normal range with nitroprusside (2,977 ± 880 to 2,087 ± 755 dynes · s · cm^{-5}/m^2; p <0.001), whereas in group 2 it decreased by a lesser amount (2,829 ± 738 to 2,541 ± 641 dynes · s · cm^{-5}/m^2; p <0.05). The aortic valve gradient (peak-to-peak) was higher initially in group 1, although the difference was not significant (74 ± 27 vs 61 ± 24 mm Hg). Small elevations were observed in the aortic valve gradient

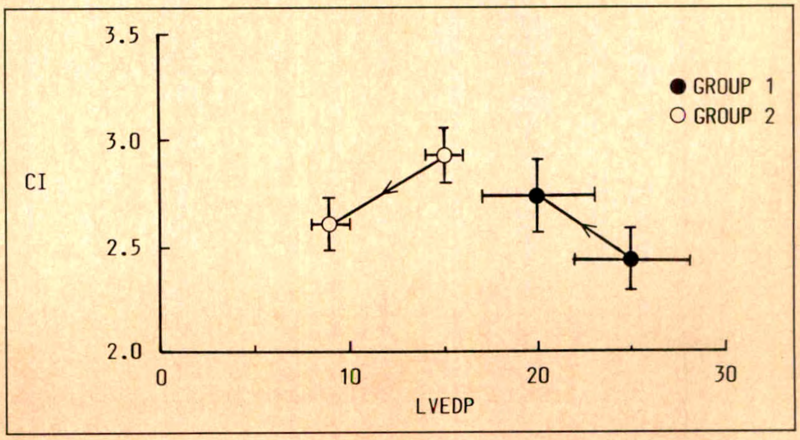

FIGURE 2. Relation between changes in cardiac index (CI, liters/min/m^2) and left ventricular end-diastolic pressure (LVEDP, mm Hg) in 35 patients with aortic stenosis before and during nitroprusside infusion. Patients are subdivided into groups 1 (cardiac index increased, *solid circles*) and 2 (cardiac index decreased, *open circles*). Changes from before to during nitroprusside are indicated by direction of *arrowhead*.

with nitroprusside infusion in both groups, but in neither group was the change significant (74 ± 24 to 80 ± 30 mm Hg in group 1, and 61 ± 24 to 69 ± 25 mm Hg in group 2). LV stroke work index changed little with nitroprusside in group 1 (80 ± 32 to 78 ± 35 g · m/m^2; p = not significant), but decreased in group 2 (102 ± 13 to 78 ± 17 g · m/m^2; $p < 0.001$).

Valvular afterload decreased slightly with nitroprusside in group 1, but increased markedly in group 2 (−4% vs +29%). Vascular overload decreased more in group 1 than in 2 (−30 vs −10%). Overall there was a net increase in afterload in group 2, and a net decrease in group 1 (Figure 6).

DISCUSSION

Our aim in this study was to determine the effects of reduction of LV loading on patients with AS and a range of LV function. Sodium nitroprusside was chosen to reduce LV loading, because it is a potent, short-acting balanced vasodilator with rapid onset of action. The data presented show significant changes in hemodynamic parameters in patients with native valvular AS subjected to acute vasodilatation. Further, we were able to identify a subgroup of patients with AS that had a favorable hemodynamic response to loading reduction, and a group that did not. Examination of the characteristics of these subgroups allows postulation of mechanisms that may explain these disparate hemodynamic responses. We divided the patients according to their cardiac index response to nitroprusside infusion. The group in which cardiac index increased was identified by higher LV filling pressures, smaller aortic valve area and impaired systolic LV function.

Preload decreased in the group as a whole with nitroprusside administration. Whereas reduction in preload would be expected to decrease symptoms of pulmo-

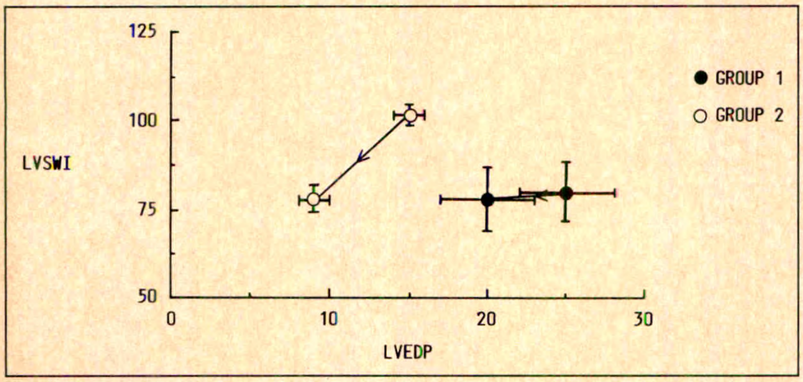

FIGURE 3. Relation between changes in left ventricular stroke work index (LVSWI, g · m/m^2) and left ventricular end-diastolic pressure (LVEDP, mm Hg) in 35 patients with aortic stenosis before and during nitroprusside infusion. Patients are subdivided into groups 1 (cardiac index increased, *solid circles*) and 2 (cardiac index decreased, *open circles*). Changes from before to during nitroprusside are indicated by direction of *arrowhead*.

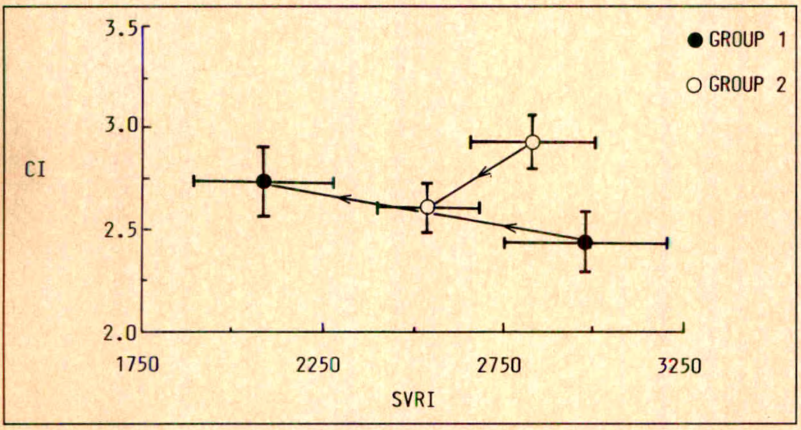

FIGURE 4. Relation between changes in cardiac index (CI, liters/min/m^2) and systemic vascular resistance index (SVRI, dynes · s · cm^{-5}/m^2) in 35 patients with aortic stenosis before and during nitroprusside infusion. Patients are subdivided into groups 1 (cardiac index increased, *solid circles*) and 2 (cardiac index decreased, *open circles*). Changes from before to during nitroprusside are indicated by direction of *arrowhead*.

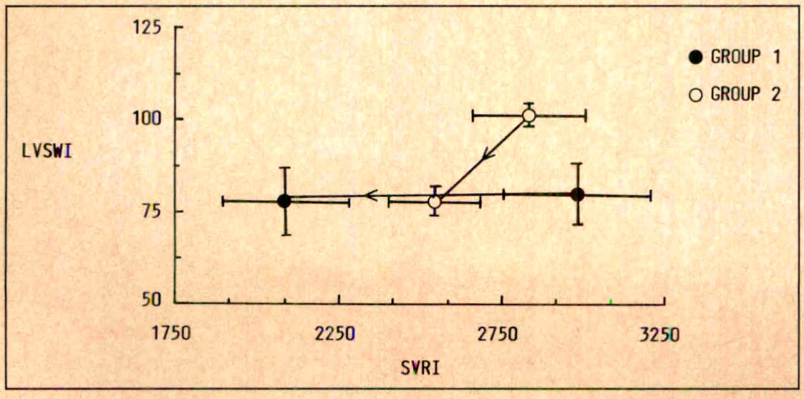

FIGURE 5. Relation between changes in left ventricular stroke work (LVSWI, g · m/m^2) and systemic vascular resistance (SVRI, dynes · s · cm^{-5}/m^2) indexes in 35 patients with aortic stenosis before and during nitroprusside infusion. Patients are subdivided into groups 1 (cardiac index increased, *solid circles*) and 2 (cardiac index decreased, *open circles*). Changes from before to during nitrprusside are indicated by direction of *arrowhead*.

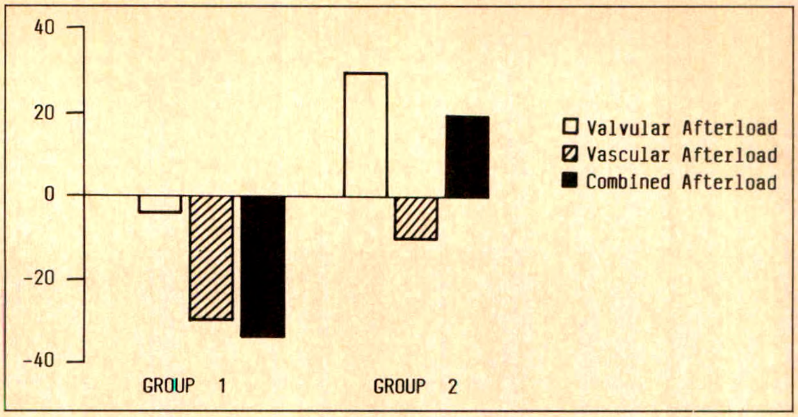

FIGURE 6. Changes in valvular, vascular and total afterload in 35 patients before and during nitroprusside infusion. Patients are subdivided into groups 1 (cardiac index increased) and 2 (cardiac index decreased). Changes are expressed as percent change from before to during nitroprusside infusion.

nary congestion, this change alone would be expected to decrease cardiac output. However, in group 1, cardiac index increased despite the reduction in preload. In the absence of any change in contractility, the increase in cardiac index observed in group 1 must be due to decreased afterload. Similar beneficial effects of vasodilatation were previously noted in patients with AS and impaired LV function.[1-4] In group 2, LV end-diastolic pressure decreased with nitroprusside, but in contrast to group 1, both cardiac and LV stroke work indexes also decreased.

The likely cause of the difference in cardiac index response of these patients lies in the LV filling pressure and its response to vasodilatation. In normal subjects, LV filling pressure ranges from 5 to 12 mm Hg,[11] and changes in LV filling pressure influence cardiac index as predicted by the Frank-Starling law of the heart.[12] In patients with AS and LV hypertrophy, a higher LV filling pressure of 22 to 35 mm Hg is present[13] and is probably needed to maintain LV diastolic filling and cardiac index in the presence of a hypertrophied, noncompliant left ventricle. In both groups, LV filling pressure decreased with vasodilatation. In group 1, filling pressure decreased to 20 mm Hg, which appeared sufficient to maintain cardiac index. In group 2, filling pressure decreased below the normal level observed in patients with AS and LV hypertrophy. This was presumably responsible for the reduction in cardiac index.

Ross[14] uses the term “preload reserve” to encapsulate the concept that preload may be increased in animals and patients with AS to increase cardiac performance to a point where there is no further benefit in terms of myocardial performance. In this study, the infusion of nitroprusside resulted in a reduction in preload to the extent that it was inadequate in the subgroup with better LV function. This dramatic decrease in cardiac performance was not previously demonstrated in patients with AS. Although a substantial reduction in LV end-diastolic pressure was observed in group 1, cardiac index increased in these patients. It may be that in this group of patients preload reached or exceeded the level at which cardiac performance is optimized (beyond the “preload reserve”), and reduction of preload in these patients did not compromise cardiac performance.

In this study we found that vascular and global afterload was reduced by nitroprusside in group 1, and cardiac index increased, presumably because the beneficial effects of afterload reduction outweighed any effect on preload reduction. In group 2, in whom cardiac index decreased presumably because of a reduction in preload to suboptimal levels, vascular afterload decreased less, and calculated valvular and total afterload increased. These changes may be due to a tendency to reflex vasoconstriction secondary to nitroprusside infusion, or to an altered balance of effects of nitroprusside on vascular pre- and afterload. The increase in valvular afterload was unexpected and may be due to changes in a dynamic component of valvular obstruction, but more probably is artefactual due to nonlinearity of thermodilution cardiac output measurements, especially at low values.[15]

We cannot completely exclude a change in myocardial contractility as a contributing factor to the observed hemodynamic changes. Nitroprusside was not shown to alter contractility, but a small increase in contractility occurs with increased heart rate.[16] However, it is unlikely that clinically significant changes in contractility occurred in these patients.

Study limitations: This was an acute intervention study, and therefore extrapolation of the results to longer term studies and the clinical situation are not possible. Myocardial contractility was not able to be assessed, but it is unlikely that significant changes occurred.

Conclusion: This study shows that in patients with AS and preserved LV function, vasodilatation resulted in decreased cardiac index. This result mandates caution in the use of vasodilators in this group of patients.

In patients with impaired LV function vasodilatation resulted in increased cardiac index, presumably because of reduction in vascular afterload without compromise from reduction in preload. This group of patients generally has a poorer prognosis, worse symptomatic status and a higher surgical risk for aortic valve replacement. The role of chronic vasodilator therapy should be evaluated in such patients.

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Value of Exercise Doppler Echocardiography in Patients with Prosthetic or Bioprosthetic Cardiac Valves

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Doppler echocardiographic evaluation of the prosthetic valve function is usually performed at rest, although this situation is not representative for patients' daily activities. Therefore, a symptom-limited Master 2-step test was performed in 61 asymptomatic patients with normal left ventricular function. No adequate Doppler signals were obtained in 5 of 61 patients (8%) within 60 seconds after termination of exercise. In patients with aortic valve prostheses (n = 24), heart rate increased from 74 ± 10 to 105 ± 18 beats/min, the maximal instantaneous gradient from 44 (range 22 to 90) to 68 (range 28 to 165) mm Hg (r = 0.89) and the mean gradient from 24 (range 12 to 50) to 39 (range 18 to 100) mm Hg (r = 0.90). In 6 of 11 patients with a maximal flow velocity ratio between the left ventricular outflow tract and the aortic valve prosthesis ≤0.25, the mean gradient increased to a value ≥50 mm Hg after exercise, whereas in patients with a ratio of ≥0.25, this never occurred. In patients with mitral valve prostheses (n = 39), heart rate increased from 80 ± 12 to 116 ± 14 beats/min and mean gradient from 6 (range 3 to 10) to 14 (range 6 to 25) mm Hg (r = 0.59). The correlation of the mean diastolic pressure gradient after exercise with pressure half-time was 0.66. Systolic pulmonary artery pressure at rest and after exercise could be determined in 22 of 39 patients (56%) and increased from 34 (range 20 to 70) to 57 (range 35 to 110) mm Hg. It is concluded that the response to exercise can, to a large extent, be inferred from Doppler parameters at rest, particularly in patients with aortic valve prostheses. The clinical implication of the high gradients found in some asymptomatic patients in the present study should be elucidated by follow-up studies.

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Doppler echocardiographic evaluation of prosthetic valve function is frequently performed at rest.[1–4] In a large simultaneous Doppler catheterization study, it has recently been demonstrated that continuous-wave Doppler ultrasound (guided by the audio signal) can accurately predict pressure gradients across mechanical prosthetic valves in both aortic and mitral positions.[5] Since the resting situation is not representative of patients' daily activities and provides only limited information on the hemodynamic consequences of a prosthetic valve, we performed a symptom-limited exercise test in asymptomatic patients with a prosthetic valve in the aortic or mitral position, or both. The objective of this study was to define the change of transprosthetic gradients with exercise in such patients and to determine its relation to Doppler echocardiographic parameters of prosthetic valve function at rest.

METHODS

The initial study group consisted of 61 patients with 29 prostheses in the aortic position and 39 in the mitral position. Inclusion criteria for this study were: functional class I or II according to the New York Heart Association criteria and a normal ventricular function on 2-dimensional echocardiography. Patients with mitral prostheses and concomitant aortic regurgitation were not admitted to the study because this could have influenced pressure half-time. Patients with aortic prostheses and a concomitant subvalvular dynamic gradient at rest were also not admitted. Patients with moderate or severe (para) valvular leakage of the prosthetic valve on clinical or Doppler echocardiographic examination were also excluded.

In 5 of 61 patients (8%), no adequate Doppler signals were obtained within 60 seconds after termination of exercise; all these patients had aortic valve prostheses. The remaining 56 patients were 21 men and 35 women, mean age 48 years (range 18 to 74). Aortic valve prostheses were present in 24 patients, and mitral valve prostheses in 39 patients. Type and sizes of the valvular prostheses are listed in Table I. Atrial fibrillation was present in 4 patients with aortic valve prostheses and in 23 patients with mitral valve prostheses.

Doppler echocardiographic examination was performed using a 2.5 or 3 MHz annular phased-array transducer interfaced with a commercially available ultrasound instrument (Vingmed, CFM 700). In addition, a nonimaging 2 MHz transducer (Pedof) was used. Left ventricular function was assessed by measurement of left ventricular size (M-mode) and estimation of global

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TABLE I Type and Size of Valvular Prostheses

	Aortic		Mitral	
	No.	Size	No.	Size*
Björk Shiley	11	21 (6) 23 (3) 27 (2)	14	25 (1) 27 (12) 31 (1)
Medtronic Hall	5	20 (1) 21 (2) 23 (1) 27 (1)	12	25 (1) 27 (10) 29 (1)
Starr Edwards	2	23 (2)	4	30 (2) 32 (1)
St. Jude Medical	2	23 (1) 25 (1)	2	27 (2)
Lillehei Kaster	1	23 (1)	2	27 (1) 29 (1)
Bioprostheses	3	21 (2) 23 (1)	5	27 (4)

*In 2 patients valve size is unknown (1 Starr Edwards and 1 Hancock prosthesis in mitral position).

ventricular performance (2-dimensional echocardiography). A conventional Doppler analysis (pulsed and continuous-wave mode) and a color Doppler flow examination was performed in each patient. Velocity profiles across the prosthetic valves were recorded from all standard transducer positions. The audio signal that contained the highest frequencies was assumed to represent the most parallel intercept between the jet and the ultrasound beam, thus yielding the maximal velocity. This point on the chest wall was marked and used again after exercise. The maximal instantaneous pressure gradient across the prosthetic valves was calculated both at rest and after termination of exercise, using the modified Bernoulli equation: $P = 4V^2$, where V = peak transprosthetic flow velocity; mean gradients were obtained by integrating the Doppler velocity signals (Vingmed CFM 700). Doppler signals were analyzed using 3 consecutive cycles for patients in sinus rhythm and 5 cardiac cycles in patients with atrial fibrillation. In patients with aortic valve prostheses, the maximal flow velocity ratio between the left ventricular outflow tract and the prosthetic valve was calculated at rest.[6,7] In patients with mitral valve prostheses, the pressure half-time was measured at rest.[8] Pulmonary artery systolic pressure was estimated both at rest and after exercise in patients with mitral valve prostheses, whenever a tricuspid regurgitation was present.[9] Exercise was performed using a symptom-limited Master 2-step. Immediately (i.e., within at least 1 minute) after termination of exercise, the patient was reexamined in the supine position. The exercise test was repeated when the patient had 2 prosthetic valves.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation and ranges. Comparison between continuous variables was performed by a paired *t* test. The significance level (p value) was determined at 0.05. The correlation between measurements at rest and after exercise, the increase in pressure gradients and the pulmonary artery pressure were assessed with linear regression analysis, using a least-squares method.

RESULTS

Aortic valve prosthesis: The maximal instantaneous gradient increased from 44 ± 19 mm Hg (range 22 to 90) at rest to 68 ± 31 mm Hg (range 28 to 165) after exercise, and the mean pressure gradient from 24 ± 11 mm Hg (range 12 to 50) to 39 ± 19 mm Hg (range 18 to 100) (Figures 1 and 2). Heart rate increased by 30 ±

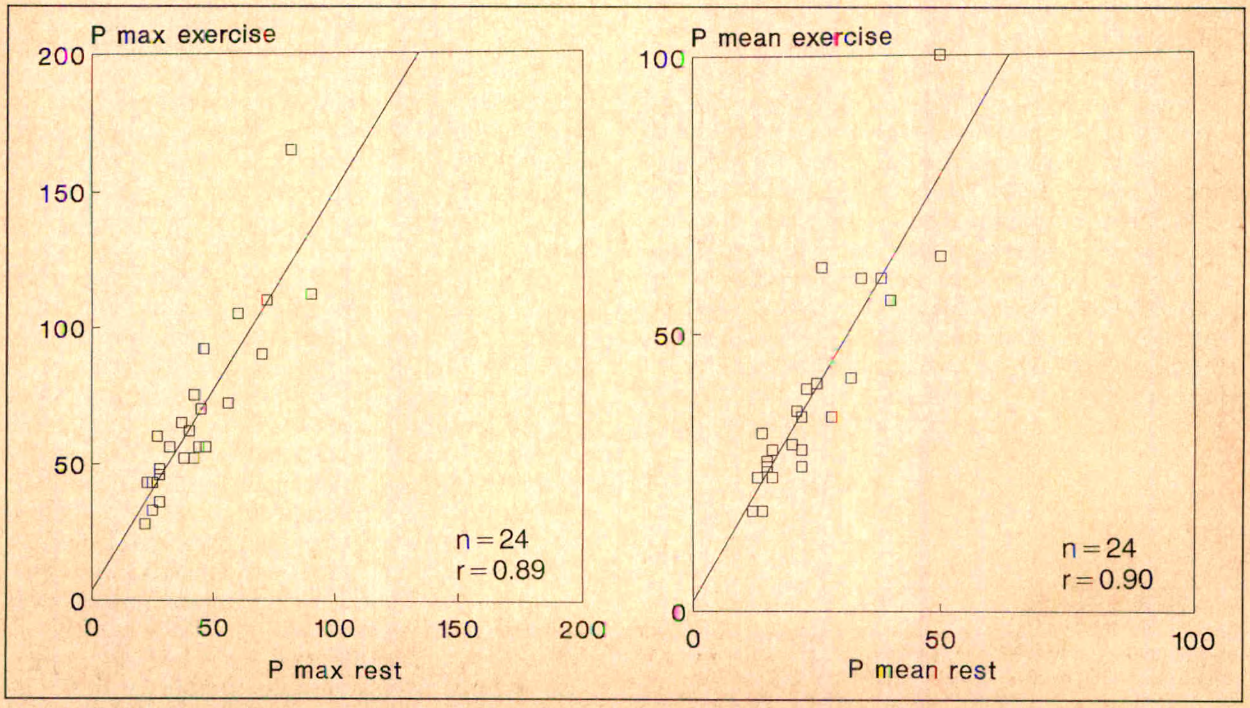

FIGURE 1. Maximal instantaneous (P max) and mean (P mean) gradient across prosthetic valves in aortic position at rest and immediately after exercise in 24 patients.

19 beats/min. There was a strong correlation between both the maximal instantaneous and mean systolic gradient at rest and after exercise: r = 0.89 and r = 0.90, respectively.

The transprosthetic gradient showed an apparent cutoff value at a ratio of approximately 0.25 both at rest and after exercise (Figure 3). In patients with a maximal flow velocity ratio ≥0.25, the mean pressure gradient never increased to values >40 mm Hg after exercise, whereas in patients with a ratio ≤0.25, the mean pressure gradient increased to values >50 mm Hg in 6 of 11 patients (Figure 3, Table II).

Mitral valve prostheses: Maximal instantaneous gradient increased from 13 ± 3 mm Hg (range 6 to 21) at rest to 25 ± 7 mm Hg (range 13 to 44) after exercise and the mean gradient from 6 ± 2 mm Hg (range 3 to 10) to 14 ± 5 mm Hg (range 6 to 25) (Figure 4). Heart rate increased by 33 ± 15 beats/min. The correlation

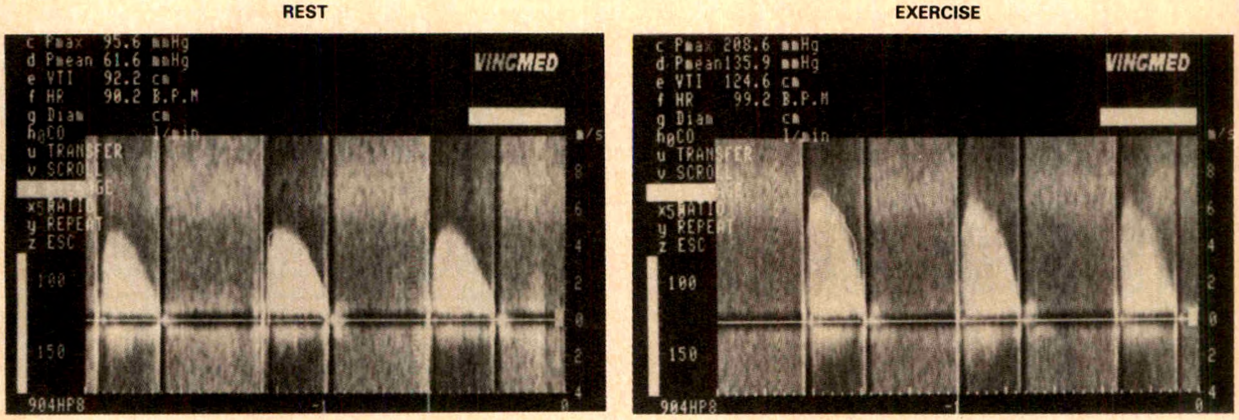

FIGURE 2. Continuous-wave recordings at rest and shortly after exercise obtained in a young asymptomatic patient with a Björk Shiley prosthesis no. 23 in the aortic position. B.P.M. = beats/min; HR = heart rate; VTI = velocity-time integral; other abbreviations as in Figure 1.

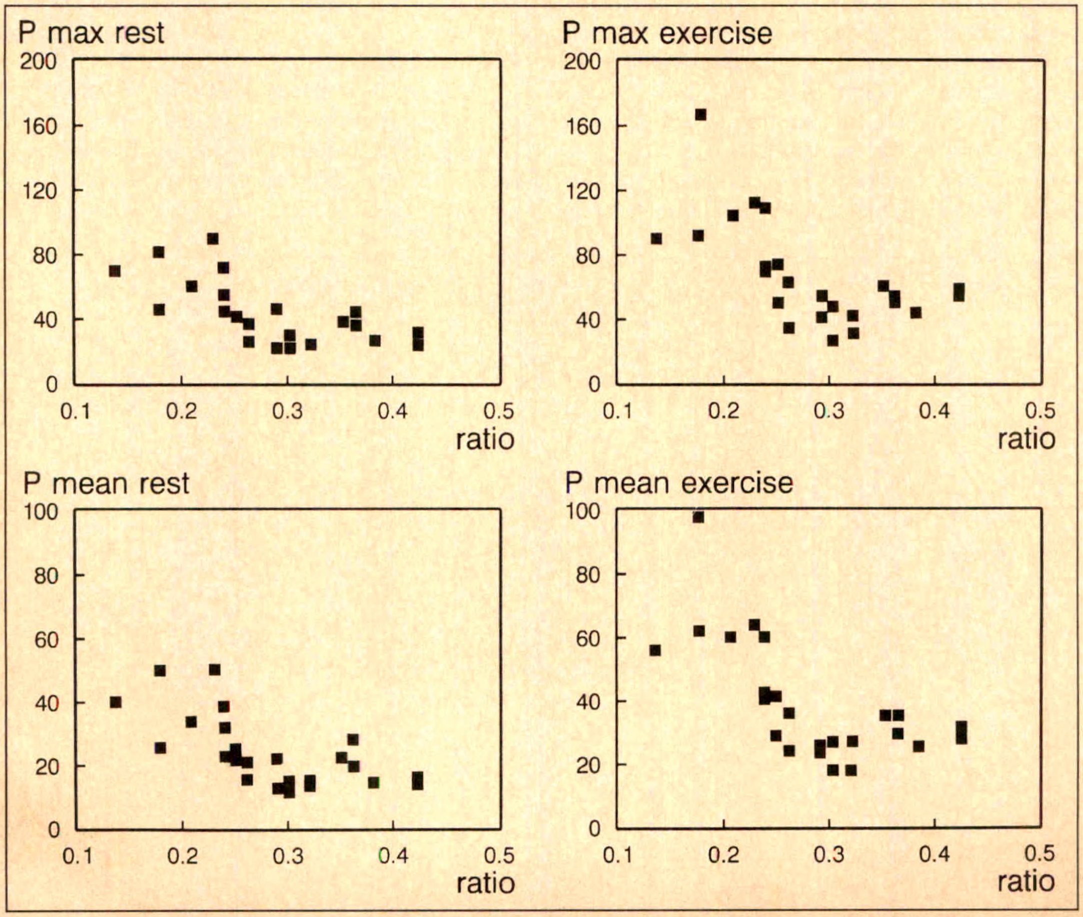

FIGURE 3. Graphic representations demonstrating the relation between maximal instantaneous (P max) and mean (P mean) transprosthetic gradient on the *y axis* and maximal flow velocity ratio between left ventricular outflow tract and prosthetic valve in aortic position on the *x axis*. Note increase in transprosthetic gradient both at rest and after exercise at a ratio ≤0.25. See text.

TABLE II Patient and Aortic Valve Prosthesis Characteristics in Relation to Maximal Flow Velocity Ratio at Rest

	≤0.25	>0.25	p Value
No. of patients	10	14	
Age (years)	43 ± 15	52 ± 19	NS
Interval surgery to Doppler*	134 (10–198)	61 (2–166)	NS
Body surface area (m^2)	1.8 ± 0.3	1.8 ± 0.3	NS
% valve size ≤21	50	43	NS
Pmax rest (mm Hg)	61 ± 16	32 ± 8	<0.0001
Pmax exercise (mm Hg)	94 ± 30	49 ± 11	<0.0001
Pmean rest (mm Hg)	34 ± 10	17 ± 4	<0.0001
Pmean exercise (mm Hg)	55 ± 19	28 ± 5	<0.0001
Valve type	5 BS; 2 MH; 2 St. Edw.; 1 LK	6 BS; 3 biopr.; 2 St. J.; 3 MH	

*Interval in months (median value and range).
biopr. = bioprosthesis; BS = Björk Shiley; LK = Lillehei Kaster; MH = Medtronic Hall; NS = not significant; Pmax = maximal instantaneous transprosthetic gradient; Pmean = mean transprosthetic gradient; St. Edw. = Starr Edwards; St. J. = St. Jude Medical.

TABLE III Doppler Characteristics of Björk Shiley, Medtronic Hall and Starr Edwards Prosthetic Valves in Mitral Position

	Björk Shiley	Medtronic Hall	Starr Edwards
No. of patients	13	11	4
Pmax			
Rest	13 ± 3	12 ± 3	14 ± 3
Exercise	25 ± 6	21 ± 5	26 ± 6
Pmean			
Rest	5.7 ± 1.6	4.6 ± 1.1	6.3 ± 0.8
Exercise	14.2 ± 4.8	10.9 ± 3.9	14 ± 3.4
Pressure half-time	105 ± 29	87 ± 20	106 ± 22
Heart rate			
Rest	79 ± 13	84 ± 9	77 ± 6
Exercise	119 ± 13	114 ± 13	113 ± 17
Syst. PAP			
Rest	36 ± 12 (11)	29 ± 5 (8)	33 ± 2 (3)
Exercise	61 ± 23 (8)	52 ± 6 (7)	50 (1)

Numbers in parentheses indicate number of patients in whom pulmonary artery pressure could be measured.
Syst. PAP = systolic pulmonary artery pressure; other abbreviations as in Table II.

between the mean diastolic gradient at rest and after exercise was moderate (r = 0.59). Table III summarizes Doppler echocardiographic findings in patients with Björk Shiley, Medtronic Hall and Starr Edwards mitral valve prostheses. There was a fair correlation between the pressure half-time at rest and the mean diastolic gradient after exercise: r = 0.66 (Figure 5). The correlation between the mean pressure gradient after exercise and heart rate increase or maximal heart rate was weak, r = 0.38 and 0.20, respectively.

Systolic pulmonary artery pressure at rest could be estimated in 29 of 39 patients (74%), and after exercise in 22 of 39 patients (56%). Systolic pulmonary artery pressure at rest was 34 ± 10 mm Hg (range 20 to 70) and after exercise 57 ± 16 mm Hg (range 35 to 110). No correlation was found between the mean pressure gradient increase after exercise and the increase in systolic pulmonary artery pressure (r = 0.35).

DISCUSSION

After valve replacement the patient's functional capacity usually improves. Compared with native valves, however, effective prosthetic valve area is smaller. This leads to "valve prosthesis–patient mismatch" (i.e., all normally functioning prosthetic valves can be consid-

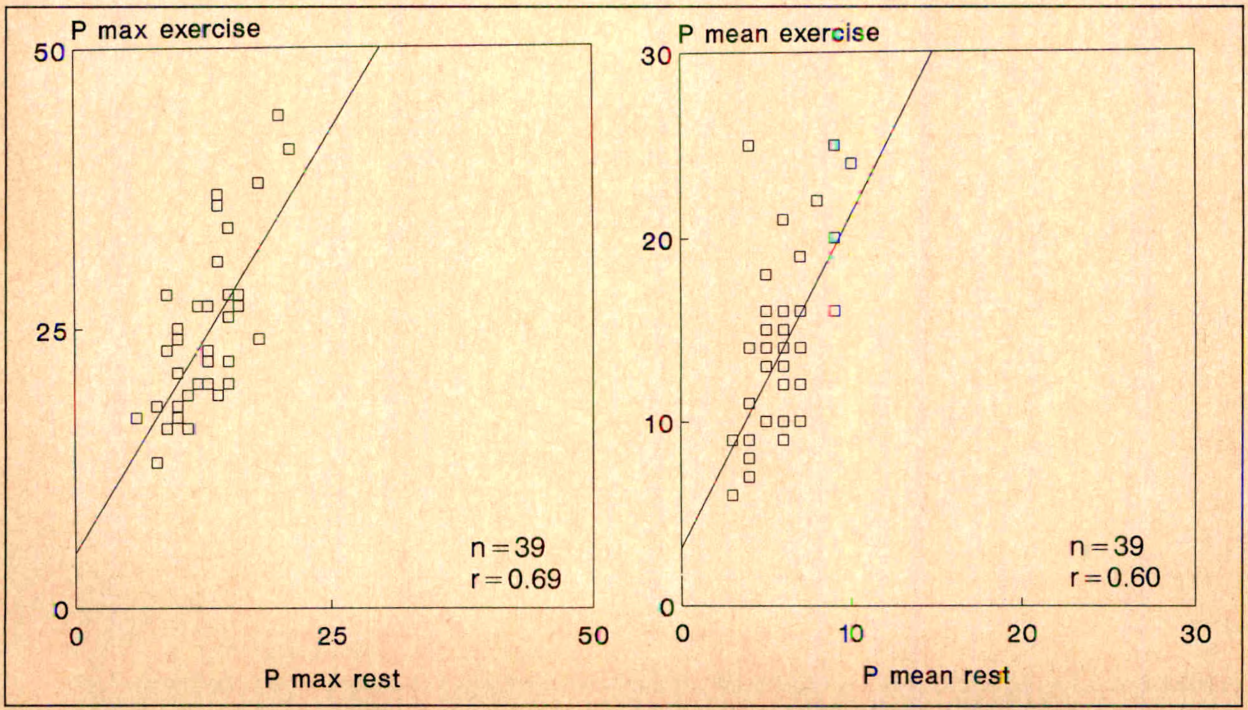

FIGURE 4. Maximal instantaneous (P max) and mean (P mean) gradient across prosthetic valves in mitral position at rest and immediately after exercise in 39 patients.

ered to be [moderately] "stenotic" compared with native valves).[10] There is only scant information on the behavior of prosthetic valves during exercise.[11-20,21] With regard to Doppler echocardiographic studies, the reason for this lack of data is the difficulty in obtaining qualitatively adequate Doppler signals during exercise because of respiratory-related artifacts and increased chest motion. Our experience is that measurements can only be performed immediately after exercise. We were not able to obtain qualitatively good Doppler signals within 60 seconds after the termination of exercise in 8% of the patients, all with aortic valve prostheses.

Aortic valve prostheses: In the present study, maximal instantaneous and mean pressure gradient at rest and after exercise were higher than those encountered in most Doppler and catheterization studies.[11-13,20,21] This is probably caused by a larger amount of smaller valve sizes (46% of our patients had a valve size ≤21 mm). In some patients with a relatively high maximal instantaneous transprosthetic gradient at rest, there was an apparent increase in this variable during exercise up to values of >150 mm Hg (Figures 1 and 2). The clinical implications of this are still unknown. The maximal instantaneous and mean pressure gradient across the aortic prosthesis after exercise correlated strongly with the pressure gradient at rest (r = 0.89 and 0.90, respectively). We also determined the value of the maximal flow velocity ratio at rest to predict the pressure gradient after exercise. This ratio was already found to be a sensitive Doppler index for detecting severe aortic stenosis (especially in patients with a decreased cardiac output), with cutoff values of 0.25 or 0.30 depending on which definition of severe aortic stenosis is applied.[6,22] In our study population, this flow ratio showed a steep increase of the transprosthetic gradient both at rest and after exercise at values ≤0.25. In 6 of 11 patients (55%) with a maximal flow velocity ratio ≤0.25, the mean pressure gradient increased to a value of >50 mm Hg after exercise, whereas this never occurred in patients with a ratio >0.25.

Mitral valve prostheses: In 77% of our patients, we found a two- to threefold increase in mean diastolic pressure gradient during exercise, which is in agreement with most Doppler and catheterization studies.[15-19] This is caused by a decrease in diastolic filling time combined with an increased transvalvular flow rate. We found only a weak correlation between mean diastolic gradient at rest and after exercise (r = 0.59). This might be due to the wide range of pressure half-time values (50 to 195 ms) at rest in our study population (Figure 5). The longer the pressure half-time at rest, the higher the value of the mean diastolic gradient across the mitral valve prosthesis, particularly after exercise. There was a weak relation between mean diastolic pressure gradient after exercise and the increase in systolic pulmonary artery pressure. This might be attributed to limitations of the technique used, i.e., the sequence of measurements, a variable response to exercise of the pulmonary vascular resistance and the limited number of observations.

Study limitations: Whenever exercise Doppler echocardiography is performed in patients with prosthetic valves, a time lag between terminating exercise and starting of measurements is inevitable; this applies both to bicycle ergometry in the supine position (where footclips have to be loosened and the patient must turn on his side before the measurements can start), and to treadmill exercise or the Master 2-step test. Obviously, the aforementioned problems would have been avoided if we had performed Doppler echocardiographic evaluation of prosthetic valves by means of pharmacologic stress testing or pacing instead of exercise. However, many catheterization studies have demonstrated that pharmacologic stress testing or pacing cannot replace exercise as a function test for native or prosthetic valves, because the hemodynamic response to exercise is composed of the effects of the tachycardia and of catecholamine stimulation.[23,24]

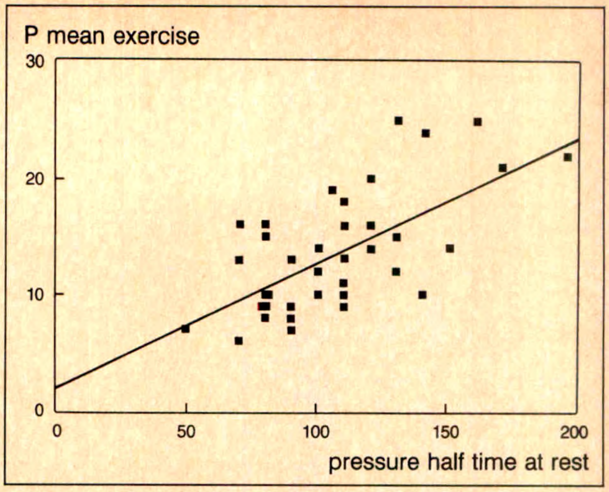

FIGURE 5. Graphic representation of the relation between mean diastolic gradient across prosthetic valves in mitral position after exercise (P mean) and the pressure half-time at rest.

Clinical implication: At present, there is no ideal Doppler echocardiographic stress test for patients with prosthetic valves, and exercise testing seems to be the most physiologic approach. Our study demonstrates that in patients with normal left ventricular function and New York Heart Association functional class I or II, the responses to exercise in those with aortic prostheses can, to a great extent, be inferred from the transprosthetic gradient and maximal flow velocity ratio at rest. This predictable response reduces the additional value of exercise Doppler echocardiography in patients with prosthetic valves in the aortic position. Since the hemodynamic response to exercise in patients with mitral prostheses is less predictable from Doppler parameters at rest, exercise Doppler echocardiography provides more relevant information for those patients.

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Influence of Mitral Regurgitation on the Response to Captopril Therapy for Congestive Heart Failure Caused by Idiopathic Dilated Cardiomyopathy

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To assess the influence of mitral regurgitation (MR) on the response to captopril therapy for congestive heart failure (CHF), 30 patients with idiopathic dilated cardiomyopathy in New York Heart Association functional class III were studied. Left ventricular end-diastolic diameter and stroke volume were measured by Doppler echocardiography, and exercise tolerance by exercise testing before and at 1, 3 and 12 months after treatment. Patients were classified into 2 groups: those with ($n = 14$) and those without ($n = 16$) MR. No significant differences were observed between the 2 groups in pretreatment studies. Exercise tolerance increased significantly in the group with MR ($p < 0.001$) during the year of follow-up, from 514 ± 193 seconds at baseline study to 671 ± 178 seconds ($p < 0.0005$) at 1 month, 688 ± 127 seconds ($p < 0.0005$) at 3 months and 690 ± 108 seconds ($p < 0.01$) at 12 months. The group without MR had no significant changes. Stroke volume increased significantly only in the MR group during follow-up ($p < 0.01$), changing from 43 ± 9 ml at baseline study to 52 ± 11 ml ($p < 0.01$) at 1 and 49 ± 11 ml ($p < 0.01$) at 3 months. At 12 months the increase was not statistically significant. Left ventricular end-diastolic diameter decreased more in the group with than without MR, although the differences were not significant. Thus, the presence of dynamic MR appears to be an important factor in the therapeutic response to captopril therapy for CHF.

(Am J Cardiol 1992;69:373–376)

Several studies have shown captopril to be an effective drug for the long-term treatment of congestive heart failure (CHF).[1–4] The clinical and hemodynamic response to therapy is variable. Whereas some patients show a marked improvement, others benefit little.[3–6] Different factors have been considered influential in the response to vasodilator treatment in CHF, but most have been questioned.[7–11] Vasodilators decrease mitral regurgitation (MR) severity probably by reducing afterload,[12–15] although other mechanisms have been proposed.[16] Since a high percentage of patients with CHF have MR,[17–19] the present study was undertaken to assess the influence of MR on the response to long-term captopril therapy for CHF.

METHODS

Patients: Thirty patients, aged 35 to 75 years (mean 60) with idiopathic dilated cardiomyopathy in CHF were studied. All had been symptomatic (New York Heart Association functional class III) for >1 year despite having received digitalis and diuretic treatment. No patient had taken vasodilators previously. All patients gave informed consent for the study.

Study design: All patients underwent Doppler echocardiography and exercise testing before treatment, and at 1, 3 and 12 months after captopril therapy. The initial dosage of captopril was 12.5 mg every 8 hours. The dosage was increased to 150 mg/day over a week if the systolic blood pressure was >95 mm Hg. Twelve patients received 75 mg/day and eighteen 150 mg/day.

Exercise test: Exercise testing was performed on a treadmill according to the Naughton protocol.[20] Exercise tolerance was measured by the maximal exercise duration. All patients had performed at least 1 exercise test before being included in the study. The supervising physician did not know the echo-Doppler results.

Doppler echocardiography: A Honeywell Ultrasound Imaging System with a 2.25 MHz mechanical transducer was used. Left ventricular end-diastolic diameter, stroke volume, MR and its severity were determined. Stroke volume was calculated[21] by the following formula: time velocity integral of left ventricle outflow × area. An average of 5 consecutive beats was considered. The aortic area was considered as πr^2, where r is half the diameter of the maximal annulus measured on the parasternal long-axis view immediately proximal to the points of insertion of the aortic leaflet during systole. Left ventricle outflow was recorded from the apical

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position at the level of the aortic annulus. The sample volume was placed in the middle of the left ventricle outflow tract, immediately proximal to the leaflet of the aortic valve. Slight adjustment was required to optimize orientation between the sample volume and flow.

MR was assessed by pulsed Doppler echocardiographic examination in the four 2-chamber apical views. Grading was assessed by the left atrial flow patterns immediately behind the mitral valve closure line and the maximal depth level of systolic left atrial flow.[22] MR was considered significant if the holosystolic flow extended, at least to the third level of the left atrium. MR was considered trivial when early systolic flow was only detected close to the mitral valve. Six patients with trivial MR and 10 without MR formed the non-MR group. The MR group was composed of 14 patients with mild to moderate MR.

Statistical analysis: The results are expressed as mean ± SD and were considered significant at $p < 0.05$. Analysis of variance for repeated measures and the paired Student's *t* test was used to assess the significance of any change in exercise tolerance, stroke volume and left ventricular end-diastolic diameter.

RESULTS

Pretreatment study: In the study before captopril therapy was begun, the non-MR group showed better exercise capacity than the MR group (578 ± 194 vs 514 ± 193 seconds), although these differences were not significant. Stroke volume was similar in both groups (42 ± 10 ml in non-MR and 43 ± 9 ml in MR group). There were also no significant differences in left ventricular end-diastolic diameter between the non-MR (74 ± 8 mm) and the MR (77 ± 6 mm) group.

Follow-up: Three patients from the MR group died in the follow-up year: 2 of the 3 died from refractory heart failure at 7 and 8 months, respectively. The remaining patient died at 2 months during gastrointestinal surgery.

Exercise tolerance: In the MR group, exercise tolerance increased significantly during follow-up ($p < 0.001$), from baseline values of 514 ± 193 to 671 ± 178 seconds ($p < 0.0005$) at 1 month, 688 ± 127 seconds ($p < 0.0005$) at 3 months and 690 ± 108 seconds ($p < 0.01$) at 12 months. The non-MR group showed no significant changes during follow-up (Figure 1).

Stroke volume: Stroke volume increased significantly in the MR group with respect to pretreatment studies ($p < 0.01$), from baseline values of 43 ± 9 to 52 ± 11 ml ($p < 0.01$) at 1 month and 49 ± 11 ml ($p < 0.01$) at 3 months. At 12 months, stroke volume was greater than at baseline study but lost statistical significance. In the non-MR group, stroke volume increased slightly with treatment, from 42 ± 10 to 44 ± 9 ml at 1 month, 43 ± 9 ml at 3 months and 43 ± 11 ml at 12 months, but these differences were not significant (Figure 2).

Left ventricular end-diastolic diameter: Left ventricular end-diastolic diameter decreased during follow-up in both groups. The differences were not significant with respect to pretreatment study at 1, 3 and 12 months in the 2 groups (Figure 3).

DISCUSSION

Captopril has proved to be an effective drug in the chronic treatment of CHF. However, although symptoms and exercise tolerance are improved, individual responses to treatment vary greatly.[3–6] Several studies have considered the influence of certain factors on the response to captopril therapy,[7–10] but none have assessed the role of MR in the response to chronic treatment of CHF. This issue may be clinically relevant since MR is present in 60 to 100% of patients with heart failure.[17–19,23] In our series, the prevalence was 47%, because only more than minimal degrees of severity were included in the MR group.

Intravenous vasodilators acutely reduce MR volume. In patients with similar left ventricular parameters,[12–14] intravenous vasodilators induce significantly greater cardiac output and lower left ventricular filling pressure in patients with dynamic MR than in those without MR. Hamilton et al[15] recently reported that acute reduction in MR with intravenous nitroprusside administration may be sustained with the long-term use of oral vasodilators.

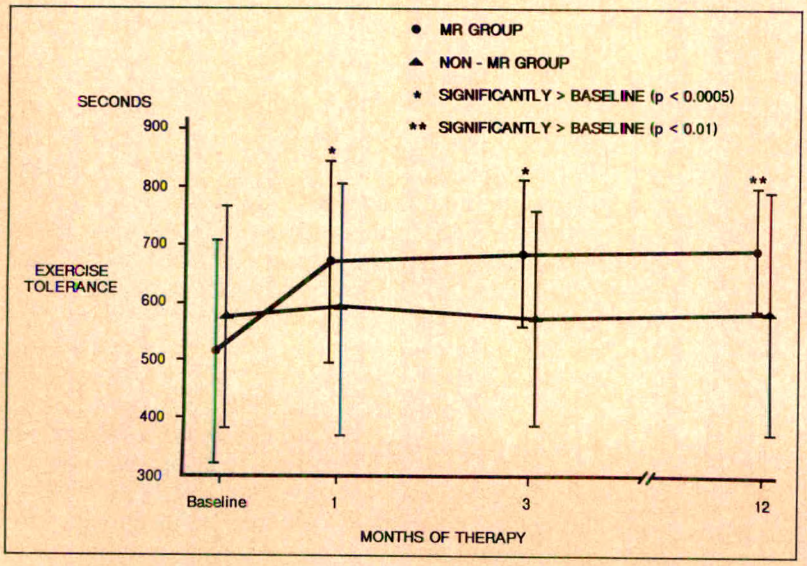

FIGURE 1. Changes in exercise tolerance with respect to pretreatment study at 1, 3 and 12 months, in groups with and without mitral regurgitation (MR).

In our series, the MR and non-MR groups had similar stroke volume and left ventricular end-diastolic diameter in the pretreatment study. Exercise tolerance was slightly higher in the non-MR group, although differences were not significant. The improvement in exercise tolerance with captopril differed according to the presence or absence of MR; thus, patients with MR had a higher increase in exercise tolerance than those without MR. This improvement was more marked at the first month of treatment and had increased slightly at 6 and 12 months. In the present study, we used the response to heart failure treatment with exercise testing because it is much more objective than the evaluation of functional class changes.[24,25]

Cardiac Doppler imaging permits satisfactory cardiac output and stroke volume quantification[21] and is useful in determining its changes secondary to vasodilator therapy.[26,27] Some studies with cardiac Doppler ultrasound have shown that intravenous vasodilators improve anterograde flow and notably reduce dynamic MR.[13,15,27,28] In this study, stroke volume increased significantly in patients with MR at 1 and 3 months, although this improvement ceased to be significant at 12 months of treatment. However, the non-MR group had no significant changes. The greatest improvement in both exercise tolerance and stroke volume was observed in the first month of therapy.

Several factors may influence improvement in exercise tolerance with vasodilator therapy, such as enhanced cardiac output, pulmonary capillary wedge pressure reduction, decrease in pulmonary arterial pressure or increased blood flow in peripheral muscle. Some investigators have shown that captopril initially improves exercise tolerance by increasing cardiac output[7] and, in the long term, by increasing peripheral muscle blood flow.[29] In our series, significant improvement in exercise tolerance in the group with MR lasted longer than the improvement in stroke volume. Therefore, any of the aforementioned factors might also play a role in this response to captopril therapy. Further studies are required to ascertain which of these factors provides greater improvement in exercise tolerance of patients with dynamic MR.

Reduction in left ventricular end-diastolic diameter was greater in the MR group; however, it was not statistically significant. Changes in this diameter are probably too small to be accurately detected by echocardiography. In agreement with other investigators,[30] we consider this parameter of little value in the evaluation of the response to heart failure treatment.

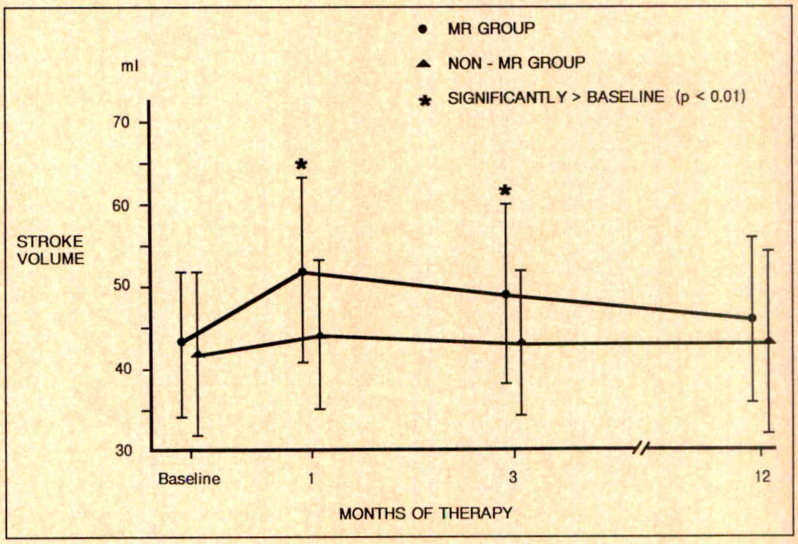

FIGURE 2. Increase in stroke volume with respect to pretreatment study in groups with and without mitral regurgitation (MR).

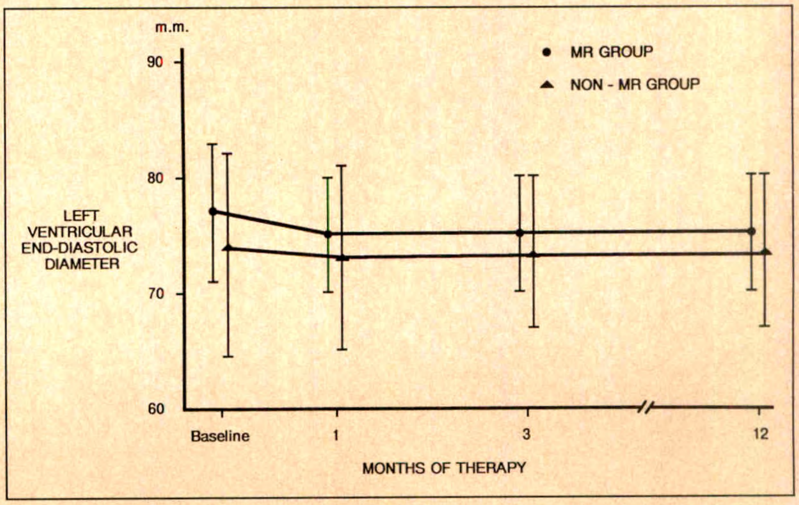

FIGURE 3. Changes in left ventricular end-diastolic diameter with respect to pretreatment study in groups with and without mitral regurgitation (MR).

The present study suggests that with captopril therapy for CHF caused by idiopathic dilated cardiomyopathy, exercise tolerance and stroke volume show greater improvement in patients with dynamic MR than in those without MR.

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Predictors of Long-Term Survival with Ebstein's Anomaly of the Tricuspid Valve

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In patients with Ebstein's anomaly of the tricuspid valve, predictors of death and indications for surgery are poorly defined. We retrospectively reviewed 48 patients with Ebstein's anomaly, 17 (35%) of whom presented in the first week of life. Duration of follow-up extended to 32 years (>10 years in 35%). Twenty of the 48 patients (42%) died, 6 in the first week of life and 1 at age 5 months. Thirteen of the 41 patients surviving to age 6 months subsequently died, 50% probability of survival being reached at 47 years. Significant ($p \leq 0.05$) predictors of death in this group were: male sex, cardiothoracic ratio ≥0.65, New York Heart Association class III or IV, breathlessness and the absence of Wolff-Parkinson-White syndrome. Eight patients died suddenly. A cardiothoracic ratio ≥0.65 was a better predictor of sudden death than functional status. All who developed atrial fibrillation died within 5 years. Other atrial arrhythmias were not helpful in predicting sudden death. In view of these findings, tricuspid valve surgery is recommended before the cardiothoracic ratio reaches 0.65, regardless of the symptomatic state.

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Ebstein's anomaly of the tricuspid valve is a rare congenital cardiac lesion with a variable degree of abnormality.[1,2] Consequently, the clinical course is also variable. In the era of tricuspid valve surgery, there has been considerable interest in the natural history of Ebstein's anomaly,[2–9] but analysis of results has been complicated by the anatomic variability, the small numbers of cases, selection of patients with bias toward particular age groups and bias toward sicker patients at presentation.[2] Although cardiomegaly,[3,7] severe symptoms[6,7] and congestive heart failure[3,6] have been considered indicators of a poor outcome, there is little information available to predict which relatively asymptomatic patients are at risk of sudden death. This review outlines the clinical course in 48 patients who had no major associated lesions.

METHODS

Seventy-three patients with Ebstein's anomaly were seen between 1950 and 1989. Twenty-five were excluded from the study because of important associated lesions: L-transposition complicated by additional anomalies in 8; pulmonary atresia or tricuspid atresia, or both, in 10; pulmonary stenosis in 3; double outlet ventricle in 2; ventricular septal defect in 1; and atrioventricular discordance in 1.

The clinical and investigative data of 48 patients who had no associated lesions, other than an interatrial communication (34 cases) or mild pulmonary stenosis (5 cases) thought not to influence outcome, were reviewed. Serial observations were available in all but 3 patients.

Univariate analysis was performed on the following variables: sex, cardiothoracic ratio, New York Heart Association functional class, symptoms of breathlessness, cyanosis, arrhythmia, Wolff-Parkinson-White syndrome, degree of tricuspid regurgitation (usually assessed on echo or cineangiocardiogram), right bundle branch block, partial right bundle branch block, P-wave pulmonale (P wave >2.5 mm in lead II), first-degree heart block, and presence of a demonstrable interatrial communication. Multivariate analysis could not be used to predict late deaths because of the small number of events. Comparisons between groups were made using the unpaired *t* test. Differences were considered significant at $2p < 0.05$. Actuarial survival was examined.[10,11]

RESULTS

Age at presentation of the 48 patients ranged from <1 day to 55 years (median 2.6 years). The sex ratio was 1:1. Twenty-five patients underwent cardiac catheterization, 8 electrophysiologic studies, 14 echocardiog-

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TABLE I Ebstein's Anomaly—Clinical Features at the Time of Presentation

	Presentation <3 Days		
	Died <10 Days (n = 6)	Survived >10 Days (n = 11)	Presentation ≥3 Months (n = 31)
New York Heart Association class			
I or II	0/6	8/11 (73%)	25/31 (81%)
III or IV	6/6 (100%)	3/11 (27%)	6/31 (19%)
Severe tricuspid incompetence	4/6 (67%)	5/9 (56%)	11/30 (37%)
Severe tricuspid stenosis	2/6 (33%)	0/9	0/30
Cardiothoracic ratio ≥0.65	4/4 (100%)	8/10 (80%)	9/28 (32%)
Mean	0.79 ± 0.06	0.71 ± 0.07	0.59 ± 0.08
Range	0.7–0.85	0.64–0.8	0.42–0.72
Electrocardiogram			
Partial right bundle branch block	1/5 (20%)	4/10 (40%)	12/31 (39%)
Right bundle branch block	4/5 (80%)	4/10 (40%)	12/31 (39%)
P pulmonale	4/5 (80%)	6/10 (60%)	13/31 (42%)
Sinus rhythm	7/7 (100%)	10/10 (100%)	29/31 (94%)
Wolff-Parkinson-White syndrome	0/7	1/10 (10%)	9/31 (29%)

Information was incomplete in some patients.

raphy, 18 operation and 15 postmortem examination. In order of reliability of assessment, the final diagnosis was based on clinical assessment alone in 1 patient, catheterization and angiocardiography in 7, echocardiography in 9, operation in 16 and postmortem examination in 15.

There were no deaths related to cardiac catheterization. Ten patients developed significant supraventricular arrhythmias: 1 accelerated junctional, 3 atrial flutter, and the remainder unspecified atrial tachycardia. One patient developed transient complete heart block. Arrhythmias triggered during electrophysiologic studies included 2 accelerated junctional, 8 orthodromic reciprocating, 2 enhanced atrial, 2 atrial flutter and 5 atrial fibrillation. Generally, only single stimuli were used. Ventricular ectopics occurred quite frequently in both types of study.

Seventeen patients (35%) presented to our hospital in the first 3 days of life, 16 with cyanosis and 1 with an asymptomatic murmur. Six (35%) of these infants died within the first week of life (Table I): 2 with severe tricuspid stenosis and 4 with severe tricuspid regurgitation. All 6 were critically ill (functional class IV), had gross cardiomegaly and died from hypoxia and congestive heart failure. Three patients who presented in functional class IV survived the first month of life. Two died at age 5 months and 9 years. The third underwent successful tricuspid valve annuloplasty at age 4 days and remains well at 2 years.

Thirty-one patients (65%) presented after age 3 months (range 3 months to 55 years, mean 19.4 ± 17.5 years). Thirteen (41%) presented with cyanosis, 12 (38%) with breathlessness, 12 (38%) with arrhythmias and 11 (34%) with asymptomatic murmurs. Ten patients presented with paroxysmal atrial tachycardia and no other symptoms. Further details are presented in Table I. At presentation, 15 of the 48 patients were in functional class III or IV with 4 others progressing to class III or IV during the period of observation.

The prognosis was similar in patients who presented in the first 3 days of life but survived to 6 months and in those who presented after 3 months. Therefore, data from the 41 patients surviving to 6 months of life were analyzed (Table II). Mean follow-up was 11 years: >10 years in 17 and >25 years in 6 patients.

There were 28 survivors at last review. Mean actuarial survival was 39 years; 50% probability of survival was reached at 47 years (Figure 1). Significant predictors of death were sex (male), last known cardiothoracic ratio ≥0.65, functional class III or IV, breathlessness, and the absence of Wolff-Parkinson-White syndrome. Neither cyanosis nor severity of tricuspid regurgitation achieved statistical significance (Table II).

Thirteen patients died after age 6 months, 8 suddenly (Table III). Whereas documented supraventricular tachycardia or cardiothoracic ratio ≥0.65, or both, predicted all sudden deaths, supraventricular arrhythmias (except atrial fibrillation) were so common in survivors that any combination including this variable had poor specificity: supraventricular tachycardia or cardiothoracic ratio ≥65%, or both, were present in 13 of 28 survivors. All 4 patients in this series who developed sustained atrial fibrillation died within 5 years. No deaths occurred in patients with Wolff-Parkinson-White syndrome. There was a close relation between cardiothoracic ratio and functional status (Figure 2). Seventy-seven percent of those dying were either in functional class III or IV or were in class II with a cardiothoracic ratio ≥0.65.

Eighteen of the 48 patients underwent 23 operations: tricuspid annuloplasty, 2; replacement, 6 with 1 repeat; Glenn procedure, 1; pulmonary valvotomy, 1; atrial septal defect closure, 3; and bypass tract division, 8 with 1 repeat. There were 2 early deaths, 1 after a Glenn procedure in 1963 in a 5-year old severely cyanotic child and the other after a pulmonary valvotomy in a moribund neonate in 1967; Ebstein's anomaly with elevated pulmonary resistance had been misdiagnosed as pulmonary atresia. Late death occurred 3 years postoperatively in a patient disabled by intraoperative cerebral air embolus.

TABLE II Ebstein's Anomaly—Details in 41 Patients Who Survived > Six Months

	Survivors (n = 28)	Deaths (n = 13)	p Value
Duration of follow-up			
Mean	10.5 ± 9.8 years	12.1 ± 10.2 years	
Range	4 months–32 years	6 months–28 years	
Age at follow-up			
Mean	21.5 ± 16.9 years	34.6 ± 20.7 years	
Range	6 months–70 years	5.3–67 years	
Male sex	11 (39%)	11 (85%)	0.03
New York Heart Association class III or IV*	1 (4%)	7 (54%)	<0.01
Breathlessness	6 (21%)	11 (85%)	<0.01
Cardiothoracic ratio ≥0.65*	4 (14%)	8 (62%)	<0.01
Severe cyanosis	2 (7%)	3 (23%)	NS
Moderate/severe tricuspid incompetence	10 (36%)	9 (69%)	NS
Wolff-Parkinson-White syndrome	10 (34%)	0	0.05
Arrhythmia	12 (43%)	8 (62%)	NS
Supraventricular tachycardia	12 (43%)	4 (31%)	NS
Sustained atrial fibrillation	0	4 (31%)	0.03
Medications	12 (43%)	7 (54%)	NS
Digoxin	8 (29%)	5 (38%)	NS
Other antiarrhythmics	8 (29%)	4 (31%)	NS
Diuretics	3 (11%)	1 (8%)	NS

*Last known.
NS = not significant.

Actuarial survival in the separate group of 25 patients with important associated lesions was 35% at 5 years (Figure 3).

DISCUSSION

Over one third of our cases presented in the first 3 days of life, similar to series previously reported.[3,8] Prognosis in these patients is very poor when the infant presents in extremis with severe cyanosis. Right heart dilatation which may be progressive[12] and death in utero are documented in fetuses with Ebstein's anomaly.[13,14] We know of no survivor after intervention for extreme tricuspid stenosis, and the only surviving newborn infant in our series with class IV symptoms and severe tricuspid regurgitation had a tricuspid annuloplasty. Prognosis in infants surviving to 6 months is similar to those presenting at a later date.

Although many have contributed to our understanding of Ebstein's anomaly, knowledge of the natural history remains incomplete.[7] In a series of 67 patients with a mean follow-up of 12 years, 61% were estimated to progress to functional class III or IV.[7] Nineteen of our patients (40%) were in class III or IV at presentation or later, significantly fewer than in the Mayo Clinic series ($p = 0.02$) but similar to that of Radford et al[8] who found on late review that 71% had no or mild symptoms.

In this series the actuarial mean survival of the 48 patients, some of whom were treated surgically, was 39 years at the time of review. Fifty percent probability of survival was reached at 47 years. This is substantially later than that reported in a pediatric series where <50% of those presenting between birth and 5 years survived to 15 years.[3] Our series is closer to a representative sample but there may be people in the community with undiagnosed minor degrees of the anomaly. Twelve of our patients were >20 years when first seen; the diagnosis in 6 was made when patients were investigated for reentrant supraventricular arrhythmias. The apparent protective effect of Wolff-Parkinson-White syndrome is presumably a statistical artifact.

The drop-off in survival in the fifth decade is in part due to sudden death (Table III). In some patients rapid supraventricular arrhythmia may be the primary event. This is poorly tolerated because of diminished right ventricular function, tricuspid regurgitation and the sudden increase in shunt at atrial level. In our series, those who died suddenly had an incidence of documented supraventricular tachycardia similar to those who survived, and none had preexcitation. In some with large hearts

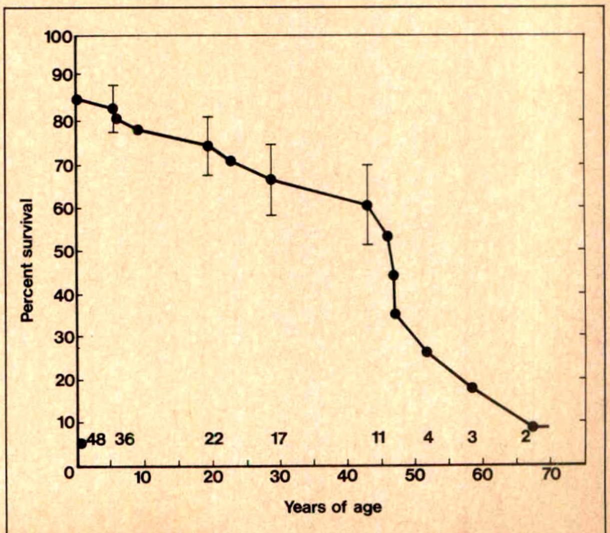

FIGURE 1. Actuarial survival in 48 patients with no major associated lesions. Numbers at risk are shown *under the curve. Black circles,* 1 or more deaths; *bars,* 1 standard deviation.

TABLE III Ebstein's Anomaly—Deaths Occurring After Age Six Months (n = 13)*

Cause of Death	Age at Presentation (yrs)	Age at Death (yrs)	NYHA Status		CTR		Previous Arrhythmia
			Presentation	Last F/U	Presentation	Last F/U	
Sudden	1 day	9.0	4	3	0.68	0.70	PAT
Sudden	8.8	19.4	2	2	0.59	0.65	0
Sudden	15.0	22.6	2	3	0.59	0.72	AF
Sudden	2.2	28.7	1	2	0.68	0.70	PAT
Sudden	20.6	46.0	1	2	0.60	0.66	AF
Sudden	42.5	67.1	—	2	0.50	0.54	PAT
Sudden	46.3	46.8	3	—	0.62	—	AF
Sudden	49.0	58.3	2	2	0.57	0.59	PAT
Postop. (Glenn)	3.0	5.8	2	4	0.60	0.67	0
Postop. (TVR)	42.9	46.9	4	4	0.70	0.70	AF
Congestive heart failure	1.6	5.3	3	4	NK	NK	0
Infective endocarditis	14.6	42.9	2	2	0.57	0.60	PAT
Coronary artery disease	46.0	51.5	3	2	0.65	—	—

*Mean age at death 36.8 ± 17.6 years.

AF = atrial fibrillation; CTR = cardiothoracic ratio; F/U = follow-up; NK = not known; NYHA = New York Heart Association; PAT = paroxysmal atrial tachycardia; Postop. = postoperative; TVR = tricuspid valve replacement; 0 = none.

the likely mode of death is a primary ventricular arrhythmia, possibly from a focus in the abnormal atrialized part of the right ventricular myocardium.[15,16] Although we accept this likelihood, our study provided no significant direct evidence. Cardiomegaly was common in those dying suddenly and other investigators[3,7] have found it to be a predictor of death. Cardiomegaly is usually a reflection of the degree of tricuspid regurgitation but, especially in the neonate, may relate to severe stenosis. In our series, tricuspid regurgitation did not emerge as a significant predictor of death, but difficulties in grading the condition, especially retrospectively, limit the usefulness of this negative observation. Certainly we would accept that important tricuspid regurgitation and progressive dilatation of the atrium and atrialized ventricle play a major role in the death of most patients.

Surgical treatment of severe Ebstein's anomaly in the neonate remains a major problem. The role of tricuspid valve annuloplasty in infancy is yet to be established.[17] Tricuspid valve replacement has been attempted in the neonatal period but results have been poor.[18] More recently, initial palliation with surgical exclusion of the right ventricle by tricuspid valve closure, atrial septectomy and an aortopulmonary shunt has been advocated in the critically ill neonate. The resultant anatomy is suitable for a Fontan procedure.[19] The role of tricuspid valve repair or replacement in the older symptomatic patient is clearly established.[17,20-22] Operation is indicated in patients with severe cyanosis or congestive heart failure. The question to address is the management of patients with cardiomegaly and minor symptoms. Information on the risk of sudden death remains scanty but we would now recommend surgery in

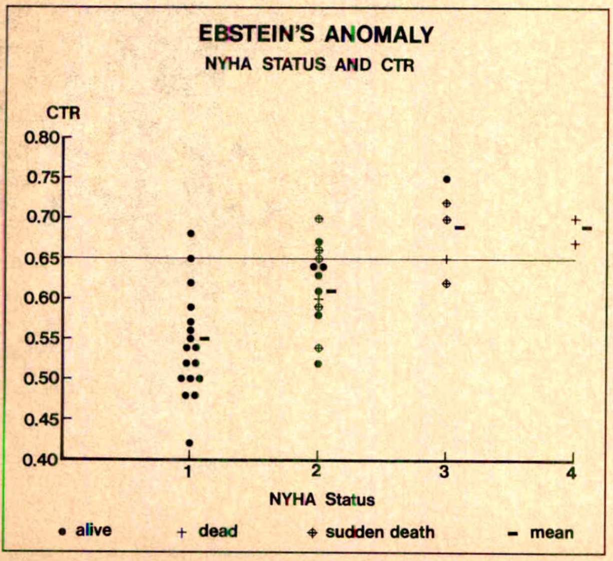

FIGURE 2. Cardiothoracic ratio (CTR) versus New York Heart Association (NYHA) functional class at last review in 37 of the 41 patients surviving >6 months.

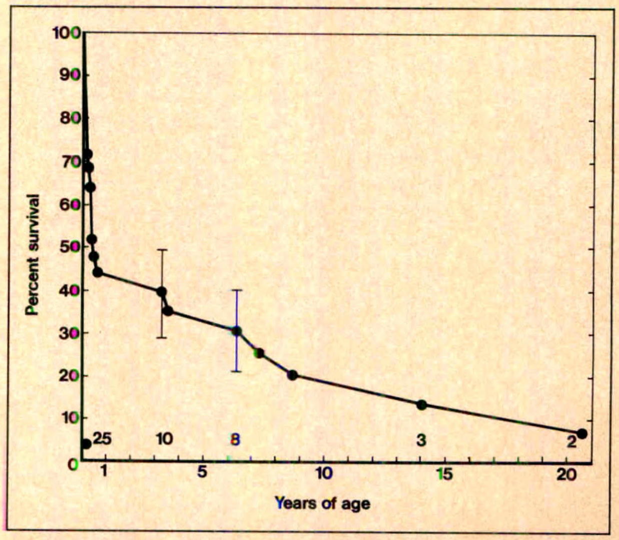

FIGURE 3. Actuarial survival in 25 patients with important associated lesions. Numbers at risk are shown *under the curve. Black circles,* 1 or more deaths; *bars,* 1 standard deviation.

a patient with class II symptoms well before the cardiothoracic ratio reaches 0.65, preferably around 0.60. Had these guidelines been used, surgery would have been performed on 6 of the 8 who died suddenly, all because of cardiomegaly but only 3 because of functional status. Three survivors would have also been recommended for surgery.

These indications for tricuspid valve surgery are similar to those suggested by Mair et al[17,22] who would operate if functional class is III or IV or on the basis of increasing cardiomegaly before the cardiothoracic ratio exceeds 0.65. Surgery now carries a relatively low risk[22] and may reduce the subsequent hazard of fatal arrhythmias. However, neither mild disease[23] nor successful surgery are totally protective against sudden death.[20] Patients with important associated lesions have a poorer prognosis[3] (Figure 3) and require different management protocols.

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Differences in Circadian Blood Pressure Between Upper and Lower Extremity in Aortic Coarctation Patients With and Without Postoperative Pressure Gradients

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The purpose of this study was to investigate possible circulatory differences between pre- and poststenotic vascular beds in postoperative coarctation patients with and without a residual pressure gradient during a physiologic decrease in circulatory activity. Simultaneous diurnal variations in blood pressure in the brachial and femoral arteries were recorded in 5 long-term postoperative coarctation patients with and in 5 without a pressure gradient. The patients were studied 6.5 to 8.5 years postoperatively with intraarterial blood pressure telemetry.

Both groups of patients had a normal pressure decrease during the hours of sleep. A significant ($p < 0.05$) increase, however, in brachial to femoral pressure gradients developed during the hours of sleep in patients with a positive gradient in contrast to patients without a gradient who had identical pressure profiles in both vascular beds. A significant positive correlation was found between changes in mean pressure gradient and upper extremity systolic pressure ($r = 0.79$, $p < 0.01$). There was no difference between the 2 groups regarding pre- and postoperative pressures, preoperative gradients or age at surgery.

Results suggest that normalization of prestenotic circadian vascular reactivity depends on complete relief of the gradient, and that upper extremity vascular abnormality may not be fully irreversible, even in older patients with coarctation.

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Studies in patients with long-term postoperative coarctation have demonstrated significant differences in reactivity between the vascular beds of the upper and lower extremities[1,2]; recently Gidding et al[3] found an increased forearm vascular reactivity to infusion of noradrenalin in long-term postoperative patients with hypertension and residual stenosis. Complete relief of the pressure gradient in coarctated dogs, however, has shown that differences in adrenergic response between the hypo- and hypertensive regions are not permanent.[4] These results suggest that the relation between brachial and femoral circulation would differ (depending on the presence or absence of residual postoperative pressure gradients) also in response to the physiologic, endogenous change in circulatory activity caused by circadian variability. This question was addressed through simultaneous intraarterial telemetric pressure recordings in the brachial and femoral arteries in long-term postoperative coarctation patients with and without a brachial to femoral pressure gradient.

METHODS

Ten patients (5 women and 5 men) were studied 6.5 to 8.5 years after repair of an isolated, juxtaductal coarctation. Half of the patients (Table I) had a positive brachial to femoral pressure gradient; the other half did not. Seven of the patients had undergone end-to-end anastomosis and 3 (nos. 3, 7 and 9, Table I) had graft insertion.

No patient received any drugs and all appeared otherwise healthy on physical examination and standard laboratory tests. Further pertinent clinical data are given in Table I. Two healthy members of the surgical staff volunteered to participate in the study and were studied under identical circumstances. The telemetric pressure recording procedure applied, described in detail elsewhere,[5] includes 2 transducers (Statham P37b, Oxnard, California), a 2-channel transmitter and receiver (Danica, Copenhagen, Denmark), and a multichannel tape recorder (Hewlett-Packard HP 3964A, Palo Alto, California). The transducers were fixed side by side to the thorax 2 cm above level of the right atrium and via two 1-m-long tubes connected to two 12-cm-long arterial catheters (Vygon, France) in the right brachial and femoral arteries, respectively. The catheters were continuously flushed with 2 to 4 ml/hour of saline solution, with heparin (10,000 IU/liter) added using a pressurized plastic bottle and 2 reduction valves

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TABLE I Clinical Data and Results from 10 Coarctation Patients With (nos. 1 to 5) and Without (nos. 6 to 10) a Positive Postoperative Brachial to Femoral Pressure Gradient and from Two Normal Control Subjects

Pt. No.	Preop. Rt. Arm BP (mm Hg)	Preop. Rt. Arm–Rt. Leg Systolic Gradient (mm Hg)	Age (yr) at:		Rt. Arm BP at Study (mm Hg)	Rt. Arm–Rt. Leg Mean Pressure Gradient (mm Hg)			
			Repair	Study		Av. Over 17 Hrs	00:30 Hrs (A)	05:30 Hrs (B)	Diff. (B − A)
1	128/85	17	10.0	17.5	115/67	4.5	4.0	6.5	2.5
2	175/100	90	19.6	26.5	144/84	4.0	7.0	11.0	4.0
3	184/94	54	18.8	27.3	174/100	1.0	1.0	16.5	15.5
4	145/85	15	32.5	39.1	140/85	2.0	−2.0	0.0	2.0
5	150/90	45	10.5	17.3	165/75	8.5	4.0	8.5	4.5
Mean	156/91	44	18.3	25.5	148/82	4.0	2.8	8.5	5.7
6	138/88	66	12.2	20.7	130/86	−4.0	−5.5	−6.5	−1.0
7	210/90	90	37.0	44.0	133/68	−3.5	−3.0	−5.0	−2.0
8	130/67	22	14.1	21.6	114/71	−8.0	−5.5	−13.5	−8.0
9	120/73	28	39.4	47.9	143/70	−3.5	−6.5	−6.0	0.5
10	176/88	86	14.2	21.9	149/89	−7.5	−16.5	−16.0	0.5
Mean	154/81	58	23.4	31.2	134/77	−5.3	−7.4	−9.4	−2.0
p value*	NS/NS	NS	NS	NS	NS/NS	<0.02	<0.02	<0.02	<0.02
Controls									
1				25.5	143/85	−2.5	−4.5	−4.0	0.5
2				42.8	123/77	−4.5	−4.0	−9.0	−5.0

*Patient nos. 1–5 vs nos. 6–10
Av. = average; BP = blood pressure; Diff. = difference; NS = not significant; Preop. = preoperative; Rt. = right.

(Sorenson). The transducer catheter telemetry lines were tested before and after the investigations for static and dynamic properties. Static response against a column of mercury was better than ±1% over the range 0 to 300 mm Hg. Values (minimum) for natural frequency were 22 Hz and 0.36 for the damping coefficient.

Blood pressures (BPs) were recorded continuously during a period of 15 to 17 hours from late afternoon until late morning. The patients were left alone in a quiet room during most of the time to keep emotional stress at a minimum. The transducers were recalibrated against a column of mercury immediately before going to bed and again as soon as the patients woke up in the morning.

The tapes were replayed at recording speed and data fed into a computer (IBM) using an analog/digital converter (IBM) with a digitizing frequency of 50 Hz per channel to give simultaneous beat-to-beat BPs in both vascular beds.

Statistical analyses were performed on hourly mean values of systolic and diastolic pressures. Mean pressure was calculated as diastolic pressure plus $\frac{1}{3}$ of the pulse pressure. Repeated-measures analysis of variance was applied when checking for significant variability in measured parameters over the entire study period and the Wilcoxon test was performed to compare pairs of pressure gradients (a pair being the gradient at the beginning and at the end of the sleeping period). Level of significance was set at $p < 0.05$.

Pressures are shown as mean ± SEM hourly. A negative pressure gradient indicates a higher pressure in the femoral than in the brachial artery.

The study was approved by the hospital ethical committee and written informed consent according to the Declaration of Helsinki was obtained from all persons involved.

RESULTS

All patients showed the familiar diurnal BP profile with a significant nocturnal decrease followed by an increase in the morning as daily activities were reassumed (Figure 1). Systolic and diastolic pressure gradients in normal volunteers and in patients with (+) and without (−) a brachial to femoral gradient are shown in Figure 2. During most of the study period (−)gradient patients, like the 2 normal subjects, had a higher femoral than brachial pressure. In (−)gradient patients and in normal subjects, only minor variations in pressure gradients were seen between 0:30 and 5:30. In contrast, (+)gradient patients had a steady increase in both systolic and diastolic pressure gradients during this period.

The change in mean pressure gradient during sleep in the individual patients and normal subjects are shown in Figure 3. A significant increase ($p < 0.05$) developed during sleep in (+)gradient patients in contrast to the nonsignificant changes in (−)gradient patients. A significant positive correlation ($p < 0.01$) was found between change in mean pressure gradient and upper extremity systolic BP at rest (Figure 4).

Patients 2 to 5 in the (+)gradient group and 9 and 10 in the (−)gradient group underwent computerized tomography of the thoracic aorta. All patients in the (+)gradient group had a stenosis at the site of repair, indicated by a 4 to 20 mm reduction in the internal aortic diameter compared with the lumen of the descending aorta. No difference between these diameters was found in the 2 (−)gradient patients, the only 2 in this group with a systolic pressure >140 mm Hg. There was no correlation between BPs or gradients and anatomic measures.

The investigation was completed without any early or late adverse effects. Drifting in excess of ±0.5 mm Hg did not occur.

DISCUSSION

Although some controversy exists over the physiologic mechanism behind diurnal BP variability, there is good evidence that a reduction in sympathetic nervous activity plays a major role in producing the nocturnal pressure decrease.[6–8] Patients with coarctation have normal levels of circulating catecholamines showing an adequate response to exercise, both before and after surgical repair.[9] This, together with the fact that all patients in this study had a normal nocturnal decrease in pressure, probably excludes any major abnormality in circadian sympathetic nervous variability. The change in baroreceptor sensitivity and setting, demonstrated in postoperative coarctation patients with mild hypertension,[10] probably modulates but does not basically alter the diurnal oscillation in BP as indicated by the normal nocturnal decrease in pressure also in our patients with high BP or residual stenosis, or both.

The significant aggravation in brachial to femoral pressure gradient during the hours of sleep, seen only in patients with a positive pressure gradient, is not likely to be caused by the obstruction to flow giving rise to the gradient. According to basic hydrodynamic laws, one would expect pressure gradients to diminish during the nocturnal period of reduced circulatory activity. This did not happen, suggesting an impaired ability of the precoarctation vascular bed to reduce vascular resistance in patients with residual gradients. Reduced vasodilatation in the arms during ischemic stress in postop-

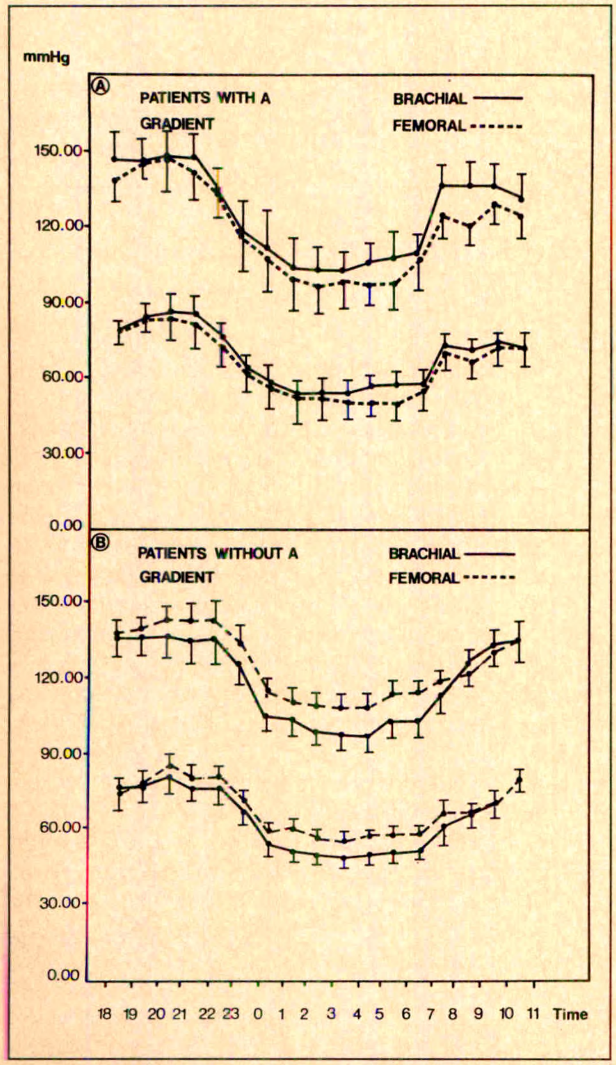

FIGURE 1. Intraarterial blood pressure profiles during 17 hours from the right brachial and femoral arteries in 5 coarctation patients with a positive brachial to femoral pressure gradient postoperatively *(A)* and in 5 patients without a gradient *(B)*. The patients in *(A)* slept from midnight until 6:30 to 7:30 A.M. The patients in *(B)* woke up between 6:30 and 8:30 A.M. Values are mean ± SEM.

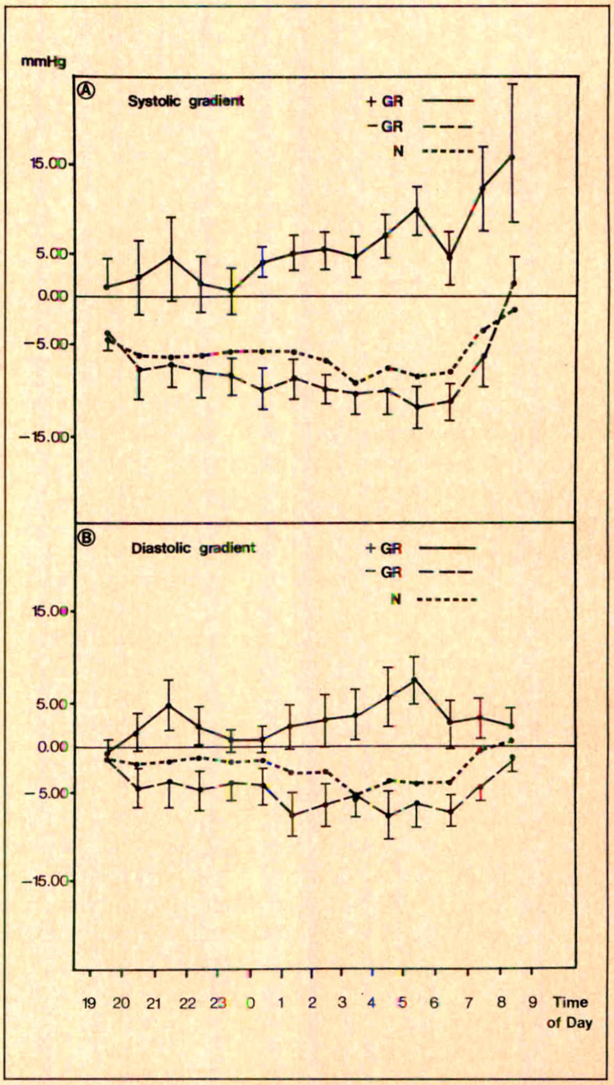

FIGURE 2. Systolic *(A)* and diastolic *(B)* pressure gradients over 13 hours in 5 patients with a positive brachial to femoral pressure gradient postoperatively (+GR), in 5 patients without a gradient (−GR) and in 2 normal control subjects (N). Values are mean ± SEM.

erative patients was also found by Šamánek et al.[1] In this study, however, neither BPs nor gradients were reported. The results of the present study also agree with those of Gidding et al[3] with regard to a residual gradient, which they associated with an abnormal vascular reactivity to noradrenalin of the arms.

Our study finally showed a significant correlation between level of BP and variability in mean pressure gradient during a period of decreasing circulatory activity.

In conclusion, restoration of normal identical variability in circadian BP in pre- and postcoarctation vascular beds appears to be dependent on complete relief of the preoperative pressure gradient. The creation of a normal, often slightly negative brachial to femoral gradient in the supine, resting patient appears to be the most important determinant in this respect, since there was no difference between the 2 patient groups in this study regarding pre- and postoperative BPs, preoperative gradients, age at repair or age at study. The results of the present study may therefore indicate that vascular abnormalities of the arms may not be fully irreversible as suggested by Gidding et al,[3] even when surgical repair is performed well beyond infancy or in adults.

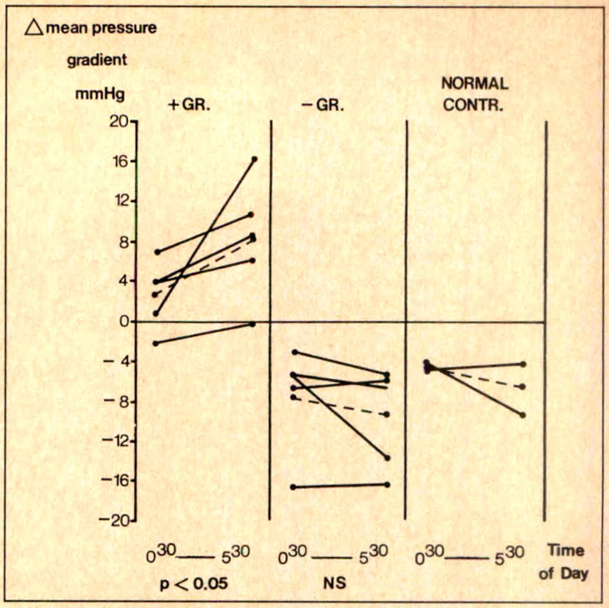

FIGURE 3. Change in mean pressure gradient during 5 hours of sleep in patients with a postoperative pressure gradient (+GR.), in patients without a gradient (−GR.) and in 2 normal control (CONTR.) subjects. NS = not significant.

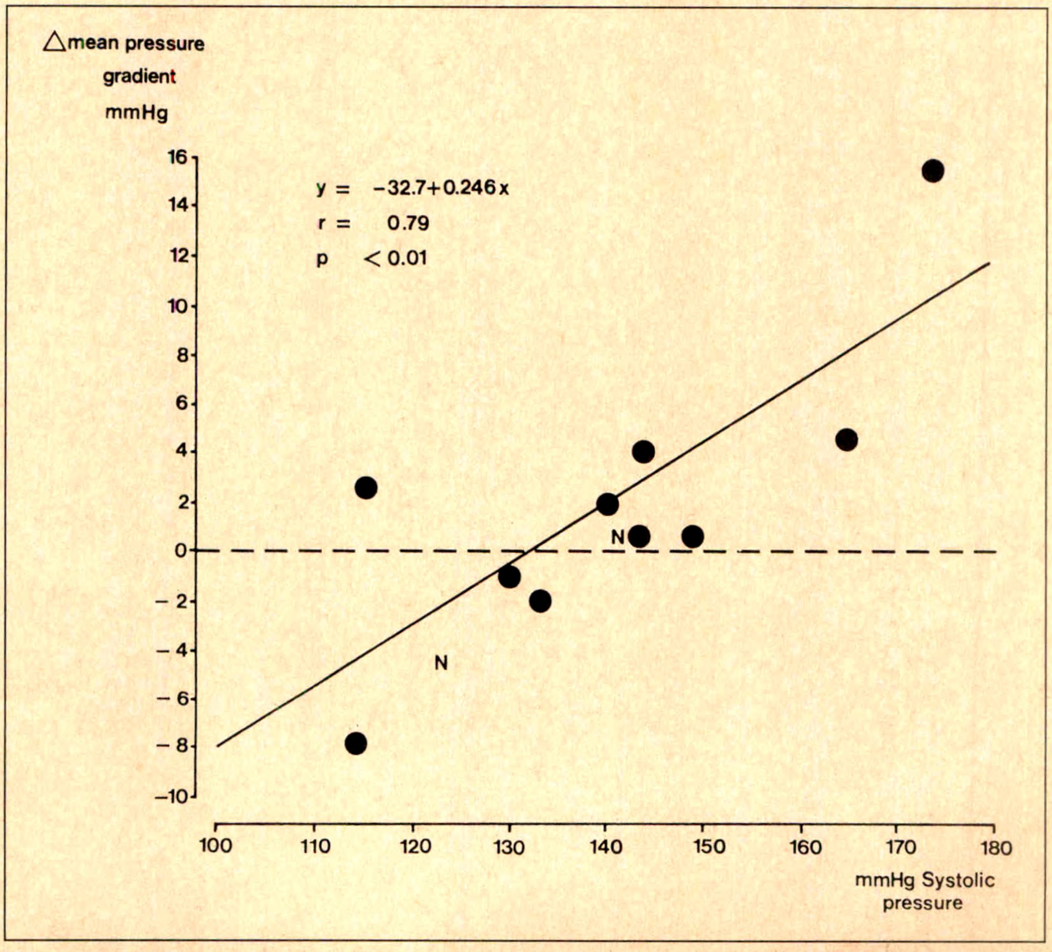

FIGURE 4. Correlation between change in mean pressure gradient during the hours of sleep and systolic pressure in the arms in 10 patients with postoperative coarctation. Values from 2 normal control subjects (N) were not included in the correlation analysis.

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Systemic Venous Flow During Cardiac Surgery Examined by Intraoperative Transesophageal Echocardiography

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Patterns of systemic venous return change after cardiac surgery. However, the exact timing and underlying mechanisms are not well understood. To analyze these changes transesophageal echocardiography was used to evaluate 21 patients (mean age 56 ± 17 years) during cardiac surgery. Eleven patients underwent coronary bypass grafting, 2 had ablation of accessory bundles, 4 had mitral and 4 had aortic valve replacements. All were in sinus rhythm and were undergoing their first cardiac operation. Hepatic and pulmonary venous flow, tricuspid annular motion, and signs of tricuspid regurgitation were recorded sequentially 5 times: (A) with chest closed, (B) with chest open and pericardium closed, (C) with both chest and pericardium open, (D) after cardiopulmonary bypass with chest open, and (E) after cardiopulmonary bypass with chest closed.

The hepatic venous Doppler flow velocity integrals (cm) changed, from stage A to stage E: systolic flow decreased from 5.9 ± 5.2 to 2.2 ± 1.4 ($p < 0.01$); diastolic flow increased from 3.1 ± 1.5 to 4.8 ± 3.3 ($p < 0.001$); and systolic to diastolic ratio decreased from 2.0 ± 1.2 to 0.7 ± 0.6 ($p < 0.001$). Reversed flow at the end of ventricular systole was present in 9 patients (43%) at stage A and in all patients at stage E. Decreased tricuspid annular motion was noted in all but 1 patient after cardiopulmonary bypass. No patient presented significant tricuspid regurgitation at any stage. In conclusion, the significant change in the pattern of systemic venous return after open heart surgery is not due to opening of the chest wall or parietal pericardium, or to tricuspid regurgitation. The decrease in tricuspid annular motion after cardiopulmonary bypass suggests abnormalities in right-sided cardiac function (stage D) and addition of mechanical restriction to cardiac motion after closure of the chest wall (stage E) as major mechanisms responsible for the observed flow changes.

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The pattern of systemic venous return changes in patients who undergo cardiac surgery supported by cardiopulmonary bypass.[1–4] These changes were first described as an alteration in jugular venous pulse contours[1] and flow velocities[2] from the normal dominant systolic flow to an equal or dominant diastolic flow. Recently, we have shown these changes are most pronounced during the first days after surgery and a tendency toward a return to normality is observed in the subsequent 6 months.[5] Also, a change in tricuspid annular motion, following the same time course, was noted and a cause-effect relation was suggested.[5] However, if and when these changes occur during surgery are not well understood. The introduction of transesophageal echocardiography as a new diagnostic tool and its use during cardiac surgery[6–8] have made it possible to observe and identify the sequence of events. The present study used intraoperative transesophageal echocardiography to observe the timing of changes in systemic venous return during open heart surgery and thereby clarify the underlying mechanisms.

METHODS

Study group: Twenty-five adult patients undergoing cardiac surgery supported by cardiopulmonary bypass were studied. None had previously undergone cardiac surgery, all were in sinus rhythm, and all had normal hepatic or superior caval venous flow velocity recordings before their operation. Only patients with sinus rhythm (18 patients) or sequential atrioventricular pacing (3 patients) after bypass were retained in the study group; thus 4 patients, 2 with complex arrhythmias and 2 with severe left ventricular failure requiring mechanical assist devices to terminate bypass, were excluded. The study population then consisted of 21 patients, 13 men and 8 women (mean age 56 ± 17 years [range 20 to 80 years]). Of these, 11 had coronary artery bypass grafts (2 also had mitral valve repair), 4 had mitral valve replacement, 4 had aortic valve replacement, and 2 had ablative surgery of accessory bundles. All subjects gave informed written consent to the protocol approved by the Committee for the Protection of Human Subjects at the Stanford University Medical Center.

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Anesthesia: High-dose narcotics with benzodiazepine and nondepolarizing muscle relaxants were used to induce and maintain general anesthesia. Fentanyl, 82 ± 23 μg/kg, was administered to 14 patients, and sufentanil, 18 ± 2 μg/kg, to 7. Muscle relaxation was achieved with pancuronium, 0.26 ± 0.1 mg/kg, in 20 patients and vecuronium, 0.7 and 0.3 mg/kg, in 2 (1 of them received pancuronium and vecuronium). Midazolam, 0.24 ± 0.06 mg/kg, was administered to all patients to assure amnesia. Induction of anesthesia was facilitated in 6 patients with etomidate, 0.15 ± 0.07 mg/kg. Eight patients received isoflurane for a portion of the period before bypass (range 15 to 150 minutes) at an inspired concentration of 0.3 to 0.6%, and 1 similarly received halothane 0.2% for 15 minutes. These agents were typically used to blunt or obviate hyperdynamic responses associated with the initial surgical incision, median sternotomy or aortic cannulation. No patient received a volatile anesthetic after cardiopulmonary bypass was terminated. Patients were mechanically ventilated with a mixture of oxygen and nitrogen. Hemodynamic control was accomplished with nitroglycerin, nitroprusside, dopamine, dobutamine, epinephrine or isoproterenol, or a combination of these.

The following factors related to anesthesia or surgery were analyzed: cardiopulmonary bypass time, type of cardioplegia, type of anesthetics, and need and use of inotropic agents to maintain adequate cardiac output immediately after bypass. During surgery, systemic arterial pressure and central venous pressure were monitored in all patients, and pulmonary artery pressure was measured in 11 patients with a Swan-Ganz catheter.

Surgery: After midline sternotomy, the pericardium was opened and the right atrium, inferior vena cava and ascending aorta were cannulated. Cardiopulmonary bypass was instituted after administration of cold myocardial preservation solution into the aortic root or directly into the coronary arteries in 19 patients (1247 ± 843 ml, range 500 to 3,200 ml). No cardioplegia was used in 2 patients. Mean total time of cardiopulmonary bypass was 117 ± 33 minutes, and mean aortic cross-clamp time was 68 ± 23 minutes. Mean bladder temperature was 29.1 ± 2.0°C. There was no significant change from before to after bypass regarding mean systemic arterial pressure (80 ± 12 to 76 ± 12 mm Hg, $p =$ not significant [NS]), mean pulmonary artery pressure (21 ± 6 to 22 ± 5 mm Hg, $p =$ NS) or central venous pressure (11 ± 4 to 12 ± 4 mm Hg, $p =$ NS). At the end of surgery the pericardium was left open in all patients. The chest was closed after placement of ≥2 chest tubes for drainage.

Transesophageal Doppler ultrasound recordings: All ultrasound recordings were obtained using a Hewlett-Packard ultrasonograph (model Sonus 500, Andover, Massachusetts) with a 5 MHz transducer mounted at the tip of a 14 mm adult gastroscope (model 21362A, HP echoscope). Studies were performed in the operating room with the patient in the supine position under general anesthesia. The echoscope was introduced into the esophagus with the transducer facing anteriorly. Tomographic planes were obtained in the usual fashion by translating and rotating the echoscope within the esophagus while observing the ultrasonic image for reference.[6] In each patient the following intraoperative recordings were obtained: hepatic and pulmonary venous flow Doppler tracings, tricuspid anterograde flow, tricuspid annular motion, and assessment of tricuspid regurgitation using Doppler color flow mapping. All recordings were made 5 times: (A) with chest closed, (B) with chest open and pericardium closed, (C) with both chest and pericardium open, (D) after cardiopulmonary bypass with chest open, and (E) after cardiopulmonary bypass with chest closed.

Recently we reported a method for visualizing the hepatic veins by transesophageal echocardiography that was used in this study.[9] The right atrium was imaged and the echoscope advanced until the entrance of the inferior cava was seen. The probe was then rotated clockwise until the hepatic veins were visualized. It was often helpful to superimpose the color flow velocity image on the 2-dimensional echocardiogram to identify the flow within the hepatic veins. The pulsed-wave Doppler sample volume was then placed in 1 of the hepatic veins and recordings were obtained. The filter was set at 50 Hz to register low-velocity signals.

Pulmonary venous flow tracings were obtained from the upper left pulmonary veins. The transducer was manipulated starting from the 4-chamber view. After the tips of the mitral valve leaflets were identified, the probe was withdrawn slightly until pulmonary veins were clearly visualized. The Doppler sample volume was placed approximately 1 to 2 cm into the pulmonary vein and pulsed-wave Doppler tracings were recorded.

Tricuspid valve anterograde flow was obtained by placing the pulsed-wave Doppler sample volume at the tips of the tricuspid valve leaflets, using the 4-chamber view. Signals were recorded when the opening and closure of the tricuspid valve could be clearly identified. Tricuspid annular motion and Doppler color flow mapping of the tricuspid valve were obtained using the same view. The electrocardiogram was recorded simultaneously. Angle correction was not used. Each study was recorded on a strip chart at 50 and 100 mm/s and videotaped for later review.

Analysis of Doppler recordings (Figure 1): Hepatic venous flow during each beat was analyzed by dividing the cardiac cycle into systole and diastole.[9,10] Systole was defined as the interval from tricuspid valve closure to tricuspid valve opening; diastole was measured from tricuspid valve opening to tricuspid valve closure. Tricuspid opening and closure were determined from the tricuspid anterograde flow using pulsed-wave Doppler ultrasound recordings and timing was referenced to the electrocardiogram. Hepatic venous flow peak velocities and flow velocity integrals were measured in both phases, the latter by manual planimetry at an average of 3 beats. Inter- and intraobserver variability, as well as reproducibility of hepatic venous flow parameters obtained by transesophageal echocardiography, were recently reported by our group.[9] The end-expiratory phase of the respiratory cycle was noted during recording and was used for selection of beats for analysis. The time to reach peak flow velocity, both in systole and diastole, was also determined, before and after cardiopulmonary

TABLE I Hepatic Venous Flow Velocities at the Five Intraoperative Stages

	Systole		Systolic Reversal		Diastole		Atrial Reversal		Systole/Diastole Ratio	
Intraoperative Condition	Peak Vel. (cm/s)	Vel. Int. (cm)	Peak Vel. (cm/s)	Vel. Int. (cm)	Peak Vel. (cm/s)	Vel. Int. (cm)	Peak Vel. (cm/s)	Vel. Int. (cm)	Peak Vel. (cm/s)	Vel. Int. (cm)
A	19 ± 15	5.9 ± 5.2	2.5 ± 3.4	0.4 ± 0.6	12 ± 9	3.1 ± 1.5	6.9 ± 3.4	1.1 ± 0.6	1.8 ± 1.3	2.0 ± 1.2
B	20 ± 11	5.6 ± 3.0	2.6 ± 4.0	0.7 ± 1.2	11 ± 7	3.2 ± 2.2	7.6 ± 2.8	1.5 ± 0.7	2.2 ± 1.5	2.3 ± 1.6
C	16 ± 9	4.6 ± 2.4	2.2 ± 4.6	0.5 ± 1.0	11 ± 6	2.8 ± 1.0	6.7 ± 3.6	1.2 ± 0.8	1.7 ± 0.7	1.8 ± 0.8
D	16 ± 11	3.1 ± 2.9	13.9 ± 8.5	2.6 ± 2.1	24 ± 12	6.1 ± 4.0	1.7 ± 4.9	0.2 ± 0.5	0.7 ± 0.4	0.7 ± 0.7
E	16 ± 10	2.2 ± 1.4	15.4 ± 9.4	3.0 ± 2.8	24 ± 11	4.8 ± 3.3	1.7 ± 4.7	0.2 ± 0.6	0.8 ± 0.8	0.7 ± 0.6

Values represent mean ± 1 standard deviation.

A = chest and pericardium closed; B = chest open and pericardium closed; C = chest and pericardium open; D = chest open after cardiopulmonary bypass; E = chest closed after cardiopulmonary bypass; Int. = integral; Vel. = velocity.

bypass, and corrected for heart rate.[11] Pulmonary venous flow during each beat was analyzed by measuring systolic and diastolic peak flow velocities and calculating the ratio between them. Heart rate was determined from the electrocardiogram.

Analysis of tricuspid annular motion and tricuspid regurgitation: Tricuspid annular motion and the presence or absence of tricuspid regurgitation were recorded at the 5 times previously described, and qualitatively analyzed. Annular motion was assessed qualitatively using 2-dimensional echocardiography and classified as normal, hypokinetic or akinetic according to the motion of its lateral aspect. Normal was defined when a distinct systolic motion of the annulus toward the apex was present; akinetic was defined when the annulus did not move during systole and hypokinetic when systolic motion was still present but decreased in relation to the baseline observation. Tricuspid regurgitation was assessed by Doppler color flow mapping and, if present, classified according to the spatial distribution of the regurgitant jet within the right atrium: trace or mild occupied <⅓ of the atrium, moderate from ⅓ to ⅔, and severe >⅔.[12] All recordings, shown in random sequence, were read for tricuspid annular motion and tricuspid regurgitation by 1 investigator who was aware of stage A but was unaware of the other stages. For data analysis, each patient served as his or her own control.

Data analysis: Peak flow velocity and velocity integrals are expressed as mean ± 1 standard deviation. Differences in mean values were compared using 2-tailed paired Student's *t* test. Differences between stages were analyzed by 2-way analysis of variance. For significant F ratios, group mean values were compared using Fisher's test. The correlation between heart rate, the different intraoperative conditions and the changes in hepatic venous flow velocity integrals was determined by stepwise linear regression analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Hepatic venous flow recordings (Table I): At stages A, B and C (before cardiopulmonary bypass), all 21 patients had biphasic hepatic venous flow by Doppler tracings, with systolic and diastolic flow toward the right atrium. In 19 patients the systolic to diastolic ratio was >1; in 2 patients a slight predominance of diastolic flow was seen. All had reversed flow coincident with atrial contraction, and 9 also showed slight flow reversal

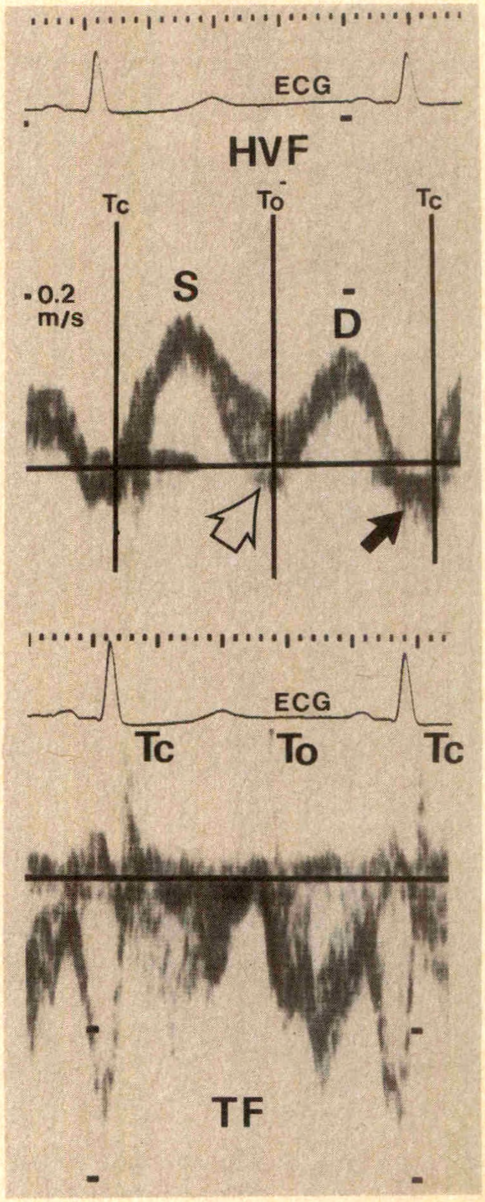

FIGURE 1. Normal pulsed-wave Doppler hepatic venous flow velocity (HVF) *(upper panel)* and tricuspid anterograde flow (TF) *(lower panel)* tracings obtained by transesophageal echocardiography. Tricuspid anterograde flow was recorded to identify systole (S) and diastole (D) using the valve opening (To) and closure (Tc) as markers. *Open arrow* indicates minimal reversed flow into the hepatic vein at the end of ventricular systole; *black arrow* indicates reversed flow associated with atrial contraction. ECG = electrocardiogram.

at the end of ventricular systole. After cardiopulmonary bypass, however, a dramatic change in flow pattern was observed with a decrease in systolic to diastolic ratios from 1.8 to 0.8 for peak flow velocities and 2.0 to 0.7 for flow velocity integrals (Figure 2). The change in wave pattern was also reflected in the timing of systolic and diastolic flow, with an earlier peak of systolic forward flow velocities after cardiopulmonary bypass (from 193 ± 42 before to 88 ± 41 ms after; $p < 0.001$) and a later peak of diastolic forward flow velocities (from 194 ± 28 before to 234 ± 62 ms after; $p < 0.02$), both corrected for heart rate.

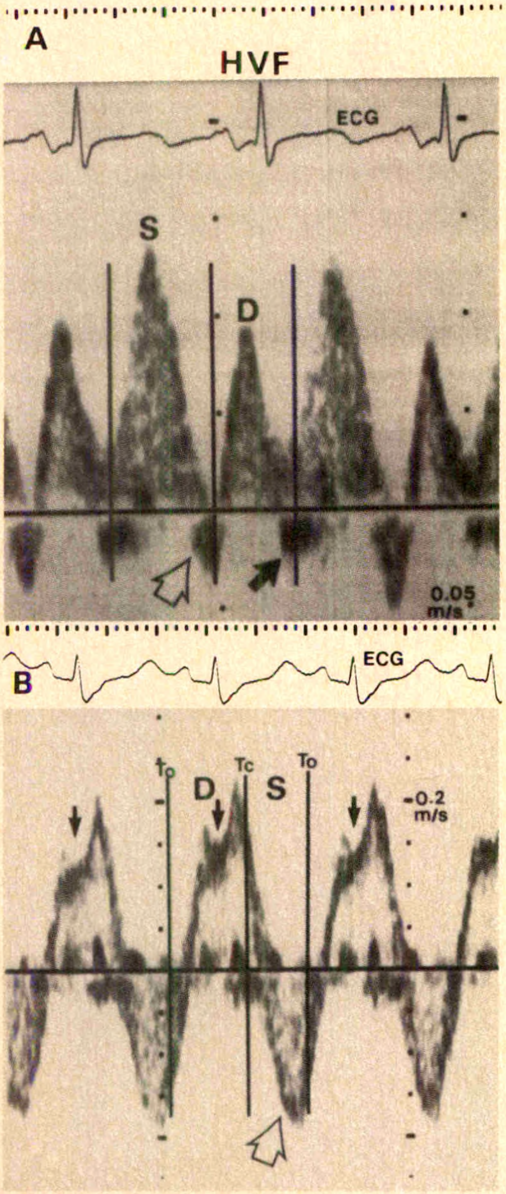

FIGURE 2. Hepatic venous flow velocity obtained before *(A)* and after cardiopulmonary bypass *(B)*. Before bypass *(A)* there is a biphasic filling pattern with a predominance of systolic component. After cardiopulmonary bypass *(B)* there is a predominance of diastolic flow, with significant reversal coincident with the end of ventricular systole. *Small black arrow* indicates notch coincident with atrial contraction. Abbreviations as in Figure 1.

Reversed flow at the end of ventricular systole, with an increase in both peak flow velocity and flow velocity integral, was seen in all patients after cardiopulmonary bypass. In contrast, reversed flow during atrial contraction was present in only 3 patients at stages D and E. In the others a discrete notch during diastolic filling, related to atrial contraction-relaxation, was observed (Figure 2). A significant increase in heart rate after cardiopulmonary bypass also was noted (63 to 97 beats/min). Regression analysis failed to show a statistically significant correlation between this increase in heart rate and any of the observed changes in hepatic venous flow velocities ($p = 0.49$).

Tricuspid annular motion (Figure 3): In 19 of 21 patients tricuspid annular motion was considered normal before cardiopulmonary bypass, at any stage (16 patients at stage A, 12 at stage B and 15 at stage C). After bypass, with the chest open, only 4 patients still had normal tricuspid annular motion, and 3 of these developed annular akinesia with closure of the chest. Only 1 patient had normal tricuspid annular motion in both stages after bypass.

Tricuspid regurgitation (Figure 4): Before cardiopulmonary bypass, 14 patients had Doppler color flow mapping recordings technically adequate for assessment of tricuspid regurgitation. Three of these showed mild regurgitation and 11 showed either trace or no regurgitation. After bypass, adequate recordings were obtained in 18 patients; 5 showed mild, 2 mild to moderate, and 11 trace or no evidence of regurgitation. No patient changed >1 grade of tricuspid regurgitation and no patient had severe regurgitation at any stage.

Pulmonary venous versus hepatic venous flow (Table II): Hepatic venous flow peak velocities were compared with pulmonary venous flow peak velocities at the 5 intraoperative stages in a group of 15 patients without evidence of mitral regurgitation, which is known to influence pulmonary venous flow tracings significantly. Hepatic venous flow in these patients showed the pattern previously described, with decreased systolic flow, increased diastolic flow, and a significant decrease in the systolic/diastolic ratio from before to after cardiopulmonary bypass. In contrast, pulmonary venous flow peak velocities showed no significant change, with predominance of systolic over diastolic flow both before and after bypass.

DISCUSSION

Changes in systemic venous return after cardiac surgery were first recognized as alterations in jugular venous pulse contours[1] and then as changes in jugular venous flow velocities.[2] More recently, studies using Doppler echocardiography showed the same kind of changes in hepatic and superior vena caval venous flow velocities.[13,14] It also is known that conditions of myocardial protection differ from the right heart to the left heart.[15,16] The consequences of these differences were considered to be partly responsible for the observed relatively greater right heart dysfunction after cardiac surgery.[16] The timing of these changes in the right heart

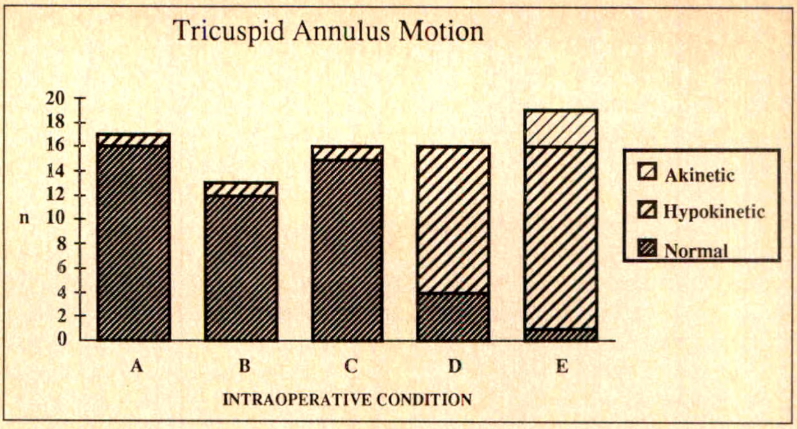

FIGURE 3. Tricuspid annular motion at the 5 different intraoperative stages. Abbreviations as in Table I.

during cardiac surgery and the factors involved have not been extensively studied. Transesophageal echocardiography is a new imaging tool for diagnosis of cardiac disease[6,8] and has proved to be an effective operating room technique in different situations,[7,8] allowing continuous monitoring without interfering with the surgical field. The present work describes its use in the study of the right heart during cardiac surgery, in order to better understand the mechanisms underlying venous flow abnormalities.

Systemic venous flow and cardiac surgery: Normal venous flow, shown by superior vena caval or hepatic venous flow recordings, has a biphasic pattern with a predominant systolic component.[4,9,17,18] There also may be small reversals of flow coincident with the end of ventricular systole and atrial contraction.[4,10,18] Systolic forward flow seems to be due to expansion of the right atrium during atrial relaxation and during ventricular systolic contraction with associated descent of the tricuspid annulus toward the apex. Diastolic forward flow is related to tricuspid valve opening and right ventricular filling, with some contribution from atrial contraction. During much of diastole, the right atrium functions as a conduit for blood from the caval veins to the right ventricle. In our study, the pattern of venous flow was essentially normal and unchanged from the first observation, early after induction of anesthesia with the chest still closed, until before cardiopulmonary bypass with the pericardium fully opened. However, immediately after bypass a dramatic change was noted, with most patients having a decrease in systolic flow — reversed flow at the end of ventricular systole — a predominant diastolic component and reversal in systolic to diastolic ratio.

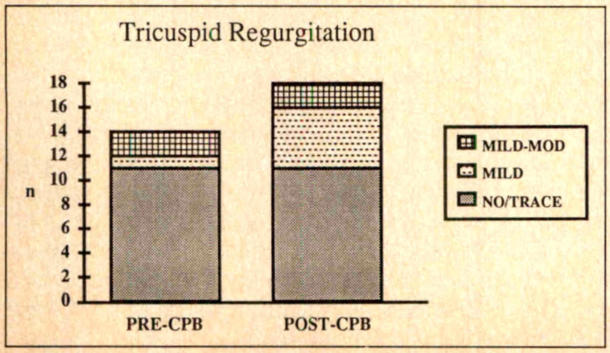

FIGURE 4. Tricuspid regurgitation in 14 patients before and in 18 patients after cardiopulmonary bypass (CPB).

This change from the normal pattern of systemic venous flow after open-heart surgery has been noted by other investigators.[3,4,13] Yoshida et al[13] compared hepatic venous flow and the external jugular vein pulse between patients who underwent cardiac surgery and patients with atrial fibrillation and tricuspid regurgitation. They found decreased or reversed systolic flow in the postoperative patients, and concluded that hepatic venous flow was not accurate in evaluating tricuspid regurgitation after cardiac surgery. Sivaciyan and Ranganathan[4] described changes in the jugular venous flow velocity patterns in a group of patients after cardiac surgery with normal right heart hemodynamics, defined as normal right heart pressures. It was suggested that these changes, consisting of equalization of systolic and diastolic flows or predominance of the diastolic component, were due to an iatrogenic decrease in compliance of the right atrium, also affecting its contractility and relaxation and thereby contributing to decreased systolic flow. The same finding was documented more recent-

TABLE II Hepatic (HVF) and Pulmonary (PVF) Venous Peak Flow Velocities in the Group of Patients Without Evidence of Mitral Regurgitation

	Systole	Diastole	S/D
HVF			
A	19 ± 17	14 ± 10	1.4 ± 0.3
B	19 ± 11	13 ± 7	1.6 ± 0.7
C	16 ± 8	12 ± 7	1.5 ± 0.6
D	17 ± 12	22 ± 12	0.8 ± 0.5
E	17 ± 11	21 ± 12	1.0 ± 0.9
PVF			
A	33 ± 18	31 ± 18	1.2 ± 0.5
B	32 ± 10	24 ± 10	1.5 ± 0.5
C	36 ± 8	25 ± 11	1.6 ± 0.5
D	37 ± 13	29 ± 11	1.4 ± 0.6
E	43 ± 15	34 ± 23	1.5 ± 0.6

Values are given as mean ± 1 standard deviation and as cm/s.
S/D = systolic to diastolic flow velocity ratio; other abbreviations as in Table I.

ly by Ranganathan et al[3] in a group of patients who underwent coronary artery bypass graft surgery.

This pattern of decreased or inverted systolic to diastolic ratio also has been described in other clinical situations, such as decreased right ventricular function, increased right ventricular end-diastolic and right atrial pressures,[4] atrial fibrillation,[4,13] significant tricuspid regurgitation[13,14,19,20] and pulmonary hypertension.[21] Recently it was shown that a decrease in systolic peak flow velocity and an increase in both diastolic and reversed flows occur during inspiration in cardiac amyloidosis, suggesting a restrictive filling pattern.[22]

The exact timing of systemic venous changes and their relation to the sequence of events occurring during open-heart surgery have not been previously documented. Our study shows that these changes occur immediately after bypass and that the pattern of venous return is normal until the heart is stopped. This suggests opening of the pericardium and cannulation of the right atrium are not major causes of the abnormal pattern in the acute setting. However, the presence of cannulas inside the right atrium might produce atrial trauma, edema, and increased right atrial stiffness. This increase in atrial stiffness, with corresponding decrease in compliance, may increase atrial relative to caval pressure and be reflected in the reversal of flow observed at the end of ventricular systole. On the other hand, the opening of the tricuspid valve and filling of the right ventricle will decrease the right atrial pressure and thus atrial filling will be predominantly observed during diastole. The absence of significant tricuspid regurgitation after cardiopulmonary bypass and of significant change in pulmonary arterial pressure excludes these as significant contributing factors to the observed changes.

Tricuspid annular motion and right ventricular function: A close correlation between tricuspid annulus plane systolic excursion measured by 2-dimensional echocardiography and radionuclide angiographic right ventricular ejection fraction has been reported.[23] Tricuspid annular motion can be quantified by either transthoracic 2-dimensional or 2-dimensional–directed M-mode echocardiography, as we have recently demonstrated.[24] However the same degree of precision is difficult to achieve using transesophageal echocardiography because of the position of the right heart chambers in relation to the planes obtained by transesophageal echocardiography. Therefore, we used a qualitative approach, considering the motion of the lateral aspect of the annulus as the reference landmark. This was selected considering that it presents the greatest motion in relation to the other annular aspects.[24] In addition each patient served as his/her own reference in the absence of standard reference values for tricuspid annular motion by transesophageal echocardiography. In our study all but 1 patient had hypokinetic or akinetic tricuspid annular motion after cardiopulmonary bypass and closure of the chest wall. This can be partially explained by decreased right ventricular function immediately after bypass. Reasons for this finding include the anterior location of the right heart, which both exposes it to radiation heat from operating room lights and positions it to receive less topical chilling, in addition to the effect of body temperature blood returning to the right atrium. All of these may cause relative right heart rewarming, thereby producing less optimal right heart myocardial preservation compared with the more posteriorly located left atrium and ventricle. The importance of these differences in myocardial preservation has been recognized.[15,16] Although it did not achieve statistical significance, there was a trend toward a decrease in both systolic and diastolic hepatic venous flow velocities and an increase in end-systolic reversal when the chest wall was closed. In our group of patients this may be due to restricted right ventricular filling imposed by mechanical right heart compression from the chest tubes, when the chest is closed. This hypothesis is reinforced in at least 3 patients in whom tricuspid annular motion became hypokinetic after chest closure. Thus, mechanical compression of the base of the right heart can be regarded as a potential additional mechanism for decreased tricuspid annulus mobility observed after chest closure. All of these factors reduce or eliminate the normal cyclic alteration in right atrial volume and may contribute to decreased systolic filling of the right atrium and reversed flow at the end of ventricular systole. These observations are further supported by studies done after Mustard or Senning operations, showing pulmonary venous flow abnormalities, similar to our findings on the systemic venous side, related to mechanical changes in the atrium secondary to the baffle procedures.[25]

Left-sided heart versus right heart changes: Pulmonary venous flow, like hepatic venous flow, normally presents a biphasic pattern with systolic and diastolic forward flow.[26,27] Left ventricular function is a prime determinant of pulmonary venous flow into the left atrium.[28] In patients with decreased left ventricular systolic function there is significant reduction in left atrial filling during ventricular systole, resulting in decreased or even reversed pulmonary venous systolic flow.[27] These changes have been attributed both to reduced mitral annular motion and loss of effective atrial contraction-relaxation.[28,29] Mitral regurgitation also decreases left atrial venous filling during systole, sometimes even producing reversed systolic flow in the pulmonary veins by Doppler recording. To assess common factors influencing alterations in the pattern of venous return to the right and left heart, the Doppler peak flow velocities of hepatic and pulmonary veins were compared both before and after cardiopulmonary bypass. Patients who had evidence of mitral regurgitation were excluded. No significant difference in pulmonary venous flow pattern was observed when recordings before and after cardiopulmonary bypass were compared. This agrees with observations showing that the pulsatile nature of pulmonary venous flow is primarily influenced by events occurring on the left side of the heart and not by forward transmission from the right ventricle through the pulmonary vasculature.[26,27] The difference in behavior between the left and right heart also may reflect better preservation of the left heart during surgery, as previously noted.

Study limitations: Patients received several types of clinically indicated drugs before, during and after surgery. For obvious ethical reasons it was not possible to have all patients under the same drug regimen. Loading conditions on the left and right heart influence Doppler flow velocities.[30,31] Thus, some of the subtle changes observed could have been influenced by pharmacologic agents. However, the presence of a persistent pattern independent of the drugs used suggests that the change in pattern is caused by factors beyond drug use or different loading conditions. Additionally, arterial, pulmonary arterial and venous pressures were essentially the same before and after cardiopulmonary bypass in these patients at the time of the recordings, although in only 11 patients was it possible to record pulmonary artery pressures.

Evaluation of tricuspid regurgitation using Doppler color flow velocity mapping in a single tomographic plane may represent an added limitation since, in some instances, the amount of tricuspid regurgitation may have been underestimated. The patients were used as their own control to minimize this problem.

Movement of the heart and liver during surgery, relative to the esophageal transducer, represents another problem when obtaining Doppler flow velocities, because the interrogation angle will change. For this reason only the systolic to diastolic ratios were used for comparison, since absolute velocities may change. There were no simultaneous intracavitary pressures recordings, although systemic arterial and central venous pressures were obtained in all patients, and pulmonary arterial pressures were available in 11 patients at the time the Doppler recordings were obtained. A limited variety of cardiac surgical procedures was included in this series.

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Relation of Plain Chest Radiographic Findings to Pulmonary Arterial Pressure and Arterial Blood Oxygen Levels in Patients with Acute Pulmonary Embolism

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Abnormalities of the plain chest radiograph of 123 patients with acute pulmonary embolism (PE) and no prior cardiac or pulmonary disease were related to the pulmonary arterial mean pressure, the partial pressure of oxygen in arterial blood, and the alveolar-arterial oxygen gradient. Patients with either a prominent central pulmonary artery or cardiomegaly had higher pulmonary arterial mean pressures than did patients with atelectasis, a pulmonary parenchymal abnormality or pleural effusion ($p < 0.001$). These radiographic findings give clues to the severity of pulmonary hypertension in acute PE and suggest that pulmonary infarction or hemorrhage is associated with less severe PE.

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Numerous investigators described the plain chest radiograph in acute pulmonary embolism (PE), and this literature was reviewed.[1] The characteristics of the plain chest radiograph in acute PE among patients with no prior cardiac or pulmonary disease also was described.[1] In such patients, the radiographic findings are not confused by prior disease. This experience has been enlarged on from data obtained from the collaborative study of the Prospective Investigation of Pulmonary Embolism Diagnosis.[2] Although the plain chest radiograph in and of itself cannot be used to diagnose or exclude PE,[3] it contributes to the noninvasive diagnostic assessment of PE through its importance in the exclusion of disease processes that may mimic PE, and by showing abnormalities that may suggest the need for further diagnostic evaluations.[1] The chest radiograph when normal in a patient who is dyspneic also may be a useful clue to the diagnosis of PE.[4] The present investigation correlates pulmonary arterial (PA) pressure and arterial blood oxygen levels with chest radiographic findings in patients with PE who had no prior cardiac or pulmonary disease, with the intent of expanding on the diagnostic information obtainable from the plain chest radiograph.

METHODS

Patient enrollment: Patients included in this investigation participated in the national collaborative study of the Prospective Investigation of Pulmonary Embolism Diagnosis. There were 2 arms of the study. One arm included only patients who volunteered for obligatory pulmonary angiograms, provided that their ventilation/perfusion scans were abnormal. The value of ventilation/perfusion scans in these patients was reported previously.[5] The second arm of the study consisted of patients who underwent pulmonary angiography at the discretion of their attending physicians. These patients were not included in the original report.[5] The present investigation includes patients with PE identified from both arms of the study.

In the present investigation, we evaluated only patients with PE who had no history or evidence of cardiac or pulmonary disease. In such patients, the manifestations related to coexistent disease were excluded. There were 123 such patients (63 men and 60 women, mean age 53 ± 17 years) with PE who had chest radiographs and a measurement of PA pressure obtained during pulmonary angiography. The diagnosis of PE

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was established by angiography in 122 patients and by autopsy in 1.

Patients were considered to have no preexisting cardiac or pulmonary disease if they had no history or evidence of valvular heart disease, coronary artery disease, myocardial infarction and "other heart disease," and if before this acute episode they had not had left- or right-sided congestive heart failure. Patients had no history of asthma, chronic obstructive pulmonary disease, interstitial lung disease and "other lung disease," and no recognized acute pneumonia or respiratory distress syndrome at the time of the evaluation for suspected PE. Patients also had no previous history of PE.

PE was considered present if the pulmonary angiogram showed obstruction of a vessel by a thrombus, the trailing edge of which could be identified, or the outline of an embolus (filling defect) within a vessel. The techniques of angiography were previously described.[5] PA mean pressure was measured with fluid-filled catheters before the injection of contrast material.

Symptoms suggestive of PE were needed within 24 hours of entry into the study. All data were obtained prospectively.

Chest radiographs were obtained within 24 hours of angiography. All images were obtained with the patient in the erect position. Chest radiographs were interpreted without knowledge of the results of pulmonary angiography. Generally accepted criteria for the interpretation of chest radiographs in clinical practice were used. Radiographic findings observed and recorded as abnormalities included: atelectasis, pulmonary parenchymal abnormality, pleural effusion, pleural-based opacity, elevated diaphragm, decreased pulmonary vascularity, prominent central PA, cardiomegaly, pulmonary edema and "other" abnormalities. Any convexity below the aortic knob, or protrusion beyond a straight imaginary line between the aorta and the left cardiac border typically denoted prominence of the main pulmonary artery. A cardiothoracic ratio >0.5 typically denoted cardiomegaly. With some allowances for poor inspiratory excursion, the same rules were used for anteroposterior projections.

Arterial blood gases and alveolar-arterial gradient: The partial pressure of oxygen in arterial blood (PaO_2) and the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) with the patient breathing room air were measured within 24 hours before the diagnostic pulmonary angiogram in 93 patients. Alveolar-arterial oxygen gradients were calculated in these patients according to standard methods.[6]

Statistical methods: Because many patients had multiple radiographic abnormalities, statistical independence among these conditions could not be assumed. As a result, a single overall comparison of PA mean pressure across all 9 listed radiographic abnormalities was not performed. Instead, PA mean pressure was evaluated for each separate pair of conditions. For each pair, a 3-group comparison was performed. These 3 comparison groups consisted of patients with both conditions, those with the first but not the second condition, and those with the second but not the first condition. If all 3 comparison groups contained ≥2 patients, then these 3 groups were compared using analysis of variance. Tukey's multiple comparison procedure was used to perform the 3 pairwise group comparisons if statistical significance was attained by analysis of variance. If only 2 of the 3 comparison groups contained ≥2 patients, then those 2 groups were compared using Student's 2-sample *t* tests.

TABLE I Pulmonary Arterial Mean Pressure and Chest Radiographic Abnormalities in 123 Patients with Acute Pulmonary Embolism

	No. (%)	PA Mean Pressure (mm Hg)
Normal	10 (8)	16 ± 5
Atelectasis or pulmonary parenchymal abnormality	94 (72)	21 ± 9
Pleural effusion	71 (55)	21 ± 10
Pleural-based opacity	45 (35)	23 ± 10
Elevated diaphragm	33 (25)	23 ± 8
Decreased pulmonary vascularity	26 (20)	24 ± 11
Prominent central pulmonary artery	20 (15)	30 ± 14
Cardiomegaly	15 (12)	34 ± 13
Westermark's sign	7 (5)	31 ± 11
Pulmonary edema	5 (4)	25 ± 10

Values are mean ± standard deviation.
PA = pulmonary arterial; Westermark's sign = prominent central pulmonary artery and decreased pulmonary vascularity.

Because each pair of conditions was analyzed separately, a comparison test was performed in each of 36 total settings. Due to this multiple testing, a reduction of the rejection level of each test was warranted. Bonferroni's multiple comparison adjustment suggested that the rejection level should be reduced from 0.05 to 0.001 (0.05 divided by 36). However, that adjustment seemed too conservative. Therefore, the standard practice of accounting for a large number of tests by lowering the rejection level of each test to 0.01 was used.

RESULTS

Radiographic abnormalities related to pulmonary arterial mean pressure: The PA mean pressures of patients with various abnormalities on the chest radiograph are listed in Table I. Results of statistical analyses of paired comparisons of PA mean pressure in patients with specific abnormalities were as follows: The lowest PA mean pressures were in patients with a normal chest radiograph. Such patients had lower PA mean pressure than did those with an elevated diaphragm ($p = 0.01$), pleural-based opacity ($p = 0.01$), decreased pulmonary vascularity ($p = 0.01$), prominent central pulmonary artery ($p = 0.001$), Westermark's sign ($p = 0.01$) or cardiomegaly ($p = 0.001$). Patients with normal chest radiographs did not have differences in PA mean pressure at levels that were considered statistically significant for this study (0.01) compared with those of patients with atelectasis ($p = 0.02$) or pleural effusion ($p = 0.03$).

The highest PA mean pressures were in patients with a prominent central pulmonary artery or cardiomegaly (Table I). Patients with a prominent central pulmonary artery had PA mean pressures higher than

TABLE II Partial Pressure of Oxygen in Arterial Blood, Alveolar-Arterial Oxygen Gradient and Chest Radiographic Abnormalities in 93 Patients with Acute Pulmonary Embolism

	No. (%)	PaO_2 (mm Hg)	A-a Gradient (mm Hg)
Normal	10 (11)	75 ± 14	30 ± 16
Atelectasis or pulmonary parenchymal abnormality	71 (76)	70 ± 13	36 ± 15
Pleural effusion	53 (57)	72 ± 15	35 ± 17
Pleural-based opacity	31 (33)	70 ± 15	37 ± 14
Elevated diaphragm	25 (27)	67 ± 12	39 ± 14
Decreased pulmonary vascularity	16 (17)	69 ± 15	39 ± 17
Prominent central pulmonary artery	11 (12)	61 ± 11	44 ± 16
Cardiomegaly	9 (10)	61 ± 16	48 ± 22
Westermark's sign	4 (4)	60 ± 14	41 ± 18
Pulmonary edema	2 (2)	55 ± 4	58 ± 2

Values are mean ± standard deviation.
A-a = alveolar-arterial; PaO_2 = partial pressure of oxygen in arterial blood; Westermark's sign = prominent central pulmonary artery and decreased pulmonary vascularity.

those of patients with atelectasis or a pulmonary parenchymal abnormality ($p = 0.001$), or pleural effusion ($p = 0.001$). Patients with cardiomegaly also had PA mean pressures higher than did those with atelectasis or a pulmonary parenchymal abnormality ($p = 0.001$), or pleural effusion ($p = 0.001$), and those with a pleural-based opacity ($p = 0.001$), elevated diaphragm ($p = 0.001$) or decreased pulmonary vascularity ($p = 0.01$). Patients with cardiomegaly and a dilated central pulmonary artery had higher PA mean pressures than did those with a prominent central pulmonary artery not accompanied by cardiomegaly ($p = 0.01$).

Radiographic abnormalities related to the partial pressure of oxygen in arterial blood, and the alveolar-arterial oxygen gradient: The PaO_2 in patients with a normal chest radiograph was higher than in those with pulmonary edema ($p = 0.009$) (Table II). The PaO_2 of patients with various other abnormalities on the chest radiograph did not differ significantly. The alveolar-arterial oxygen gradient was higher in patients with pulmonary edema than in those with a normal chest radiograph ($p = 0.001$), elevated diaphragm ($p = 0.001$) or decreased pulmonary vascularity ($p = 0.001$).

DISCUSSION

A prominent central pulmonary artery or a dilated heart on the plain chest radiograph of a patient with acute PE and no prior cardiac or pulmonary disease indicated a higher PA mean pressure than that observed in those with atelectasis, a pulmonary parenchymal abnormality or pleural effusion. Patients with normal chest radiographs had the lowest PA mean pressures. Therefore, the plain chest radiograph assists in the assessment of the severity of pulmonary hypertension in acute PE.

The observation that atelectasis, a pulmonary parenchymal abnormality or pleural effusion was associated with lower pressures than was cardiomegaly or a prominent pulmonary artery is compatible with the previous observation of other investigators that pulmonary infarction or hemorrhage (defined as the abrupt onset of pleuritic pain with or without hemoptysis and infiltrate on the chest radiograph) occurred infrequently when emboli obstructed the central pulmonary artery.[7] However, pulmonary infarction was frequent when distal arteries were occluded.[7] Presumably, patients with central PA occlusion had higher PA pressures, but this was not assessed.

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Level and Diurnal Variations of Hormones of Interest to the Cardiovascular System in Patients with Heart Transplants

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The lack of a nocturnal decrease in blood pressure in cyclosporine-treated cardiac transplant recipients may indicate abnormalities in the mechanism(s) responsible for circadian variability in other physiologic parameters such as in circulating hormones.

This possibility was addressed through repeated determinations of circulating catecholamines, neuropeptide Y, pancreatic polypeptide, calcitonin gene-related peptide, plasma renin activity, aldosterone, atrial natriuretic factor and cortisol. The results from 10 patients with heart transplants were compared with those of 12 age-matched, healthy control subjects. Both groups were studied during 24-hour supine rest.

There was no difference between patients and control subjects in mean levels of catecholamines, neuropeptide Y, pancreatic polypeptide and aldosterone. Patients had higher levels (±SD) of plasma renin activity (6.4 ± 1.3 vs 2.6 ± 0.4 ng/ml/hour, $p < 0.01$), calcitonin gene-related peptide (47.7 ± 9.9 vs 33.3 ± 5.7 pmol/liter, $p < 0.01$) and atrial natriuretic factor (93.0 ± 56.7 vs 20.7 ± 8.9 pg/ml, $p < 0.001$) than control subjects, respectively. Cortisol was not detected in patients. Abnormal diurnal profiles in patients were found for calcitonin gene-related peptide, aldosterone and atrial natriuretic factor, and for pancreatic polypeptide, together with decreased levels, in patients with >6 months follow-up.

Except for hormones reflecting sympathetic nervous activity, all hormonal systems studied showed abnormalities in level or circadian rhythmicity, or both. The pancreatic polypeptide results suggest that parasympathetic neuropathy could develop in cyclosporine-treated heart transplant recipients.

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Whereas the development of hypertension is a well-known complication in cyclosporin A-treated patients who have undergone cardiac transplantation, recent studies have shown an additional abnormality in 24-hour blood pressure regulation.[1,2]

Because information on the hormonal status in patients with heart transplants is incomplete and circadian studies have not yet been published, it remains questionable whether these patients also have abnormalities in the 24-hour variability in hormones of interest to the cardiovascular system.

This possibility was addressed through repeated determinations of circulating noradrenaline, adrenaline, dopamine, neuropeptide Y, pancreatic polypeptide, calcitonin gene-related peptide, plasma renin activity, aldosterone, atrial natriuretic factor and cortisol during a 24-hour period of supine rest in patients with heart transplants. The results were compared with those of age-matched normal healthy volunteers.

METHODS

Patients: Ten orthotopic heart transplant recipients (3 women and 7 men) with good renal function and blood pressure <160/100 mm Hg were studied. Mean age was 36 years (range 22 to 59) and mean length of time from operation to study was 1 year (range 1 month to 3.5 years). Mean age of the 12 control subjects (6 women and 6 men) was 33 years (range 20 to 58).

All patients were asymptomatic and free of signs of rejection in the most recent biopsy sample. All received cyclosporine and prednisolone (140 ± 30 mg and 5 ± 2.5 mg twice daily, respectively. One patient, however, received 30 mg of prednisolone twice a day). Six patients also received azathioprine. Antihypertensive medication (3 patients) was discontinued 24 hours before the study in the 2 patients receiving furosemide but not in the patient who received a calcium antagonist (diltiazem) because of interference with blood levels of cyclosporine.

Mean serum creatinine was 1.15 mg/dl (range 0.8 to 1.6). In 6 patients the level was within normal range of 0.5 to 1.1 mg/dl. Normal left ventricular ejection fraction was found in all patients at the latest catheterization. Mean right atrial pressure was 9.2 mm Hg (range 5 to 13). In half of the patients right atrial pressure was within normal range (−1 to 8 mm Hg). Modest tricuspid insufficiency was found in 7 patients. In the control group all appeared healthy at physical examination and standard laboratory tests.

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Both patients and control subjects were asked not to smoke tobacco and drink alcohol 6 and 72 hours before the investigation, respectively.

Study protocol: The patients (controls) were put to bed in a quiet room; a 16-gauge cannula was inserted in the left antecubital vein and, via a stopcock, connected to a pressurized bottle of 5% glucose with the addition of 10,000 U/liter of heparin. A reduction valve (Securi-Flo, von Berg, Federal Republic of Germany) allowed a continuous infusion of 2 to 4 ml/hour.

Right arm blood pressure and heart rate were recorded automatically with a self-inflating cuff instrument (Spacelabs, Redmond, Washington). No dietary restrictions were made and both patients and controls received standard hospital meals in bed, at breakfast, lunch, and dinner around 9 A.M., and 1 and 7 P.M., respectively.

Blood pressure and heart rate were recorded every 15 minutes during the daytime and every 30 minutes during the night period between midnight and 6 A.M. Blood samples were obtained every 45 minutes for the determination of neurohormones and every 90 minutes for other hormones. Emotional stress was kept at a minimum, and only the investigator was allowed entrance to the study room.

All blood samples were obtained in prechilled tubes with ethylene diaminetetraacetic acid added for noradrenaline, adrenaline, dopamine, plasma renin activity, aldosterone and cortisol. Ethylene diaminetetraacetic acid and aprotinin ("Trasylol," Bayer, Federal Republic of Germany) were added for the determination of atrial natriuretic factor, and heparin and aprotinin were added for pancreatic polypeptide and neuropeptide Y. Immediately after being drawn, the blood was centrifuged for 10 minutes at 3,000 rpm, and 4°C and the plasma stored at −80°C for later analysis. Blood for measurement of serum calcitonin gene-related peptide was centrifuged after 2 hours of coagulation and then frozen.

A total of 380 to 400 ml of whole blood was drawn over a 24-hour study period. No adverse effects were seen and all patients were well and comfortable after the investigation.

The study was approved by the hospital ethical committee. All patients and control subjects gave written informed consent according to the Declaration of Helsinki.

Laboratory procedures: Plasma noradrenaline, adrenaline and dopamine were measured by high-pressure liquid chromatography according to a previously described technique.[3] Variability was 7%. Detection limit for noradrenaline and adrenaline was 10 pg/ml and for dopamine 20 pg/ml.

Plasma renin activity was measured by our own modification[4] of the method of Haber et al[5] using the constituents of a radioimmunoassay kit from NEN (Billerica, Massachusetts).

Plasma aldosterone was measured using a CIS radioimmunoassay kit from Compagnie Oris Industrie (Gif-sur-Yvette, France). The sensitivity of the direct assay was 0.07 nmol/liter. Intra- and interassay variability was 8.2 and 10.4%, respectively.

Plasma cortisol was measured using CEA Sorin kits (Saluggia, Vercelli, Italy). The sensitivity of the assay was 15 to 20 nmol/liter. The intraassay variability varied between 5.4 and 3.9% and interassay variability between 9.6 and 5.5% (levels between 100 and 1,000 nmol/liter, respectively).

Plasma cortisol (and prednisolone) were (re)measured by a high-pressure liquid chromatography procedure previously described in detail.[6]

Atrial natriuretic factor was determined by a radioimmunoassay kit from Peninsula Laboratories (Belmont, California) following an extraction procedure on Sep-Pak C-18 cartridges (Waters Chromatography Division, Milford, Massachusetts). The sensitivity varied between 5 and 8 pg/ml. Intra- and interassay variability was 7.3 and 8.3%, respectively.

Pancreatic polypeptide was measured by radioimmunoassay. The minimal detectable concentration was 2.8 pmol/liter, intraassay coefficient of variation was 6.8 to 8.0% and interassay coefficient of variation was 12.8% as previously described.[7]

Neuropeptide Y was measured by radioimmunoassay as outlined elsewhere.[8] The minimal detectable level was 20 pmol/liter. The intra- and interassay coefficient of variation was 7.4 and 13.3%, respectively.

Calcitonin gene-related peptide was measured in serum using a recently described radioimmunoassay procedure.[9] Intra- and interassay variability was 4 and 7%, respectively. Detection limit was <1 pmol/liter.

Statistical analysis: Statistical analysis was performed using the Mann-Whitney test for comparison of groups. The Martinez-Iglewicz test for departure from normality, followed by repeated analyses of variance and Duncans test, were used when comparing 24-hour levels. If data did not show normal distribution, calculations were performed after logarithmic transformation.

The level of significance was set at $p < 0.05$. Lack of significance is indicated as p = not significant (NS). Values are given as mean ± SD for the hormones and as hourly mean ± SD for blood pressure and heart rate if not otherwise stated.

RESULTS

Systolic and diastolic arterial pressures and heart rate were significantly higher ($p < 0.01$) in patients with heart transplants than in age-matched normal control subjects (mean transverse values: 127 ± 13/84 ± 11 mm Hg and 90 ± 9 beats/min vs 111 ± 6/69 ± 6 mm Hg and 66 ± 5 beats/min, respectively). While patients only had minor, statistically insignificant, diurnal variations in pressure, the 24-hour heart rate profile appeared normal showing a pronounced and significant circadian variability ($p < 0.01$).

In most of the samples, from both groups studied, plasma adrenaline was below the detection limit of 10 pg/ml. However, measurable levels did not differ between patients and control subjects: mean value for patients, 51.2 pg/ml (range 24.1 to 64.2); and mean value for controls, 36.2 pg/ml (range 14.8 to 63).

Plasma dopamine was always below the detection level of 20 pg/ml in both patients and controls.

Plasma noradrenaline was normal in patients both in levels and in circadian variability (p <0.01). Mean transverse value was 227.9 ± 96.3 vs 222.6 ± 81.3 pg/ml in control subjects (p = NS).

Plasma renin activity was significantly higher in patients than in controls (6.4 ± 1.3 vs 2.6 ± 0.4 ng/ml/hour, respectively, p <0.01). Significant diurnal variability was seen neither in the former nor in the latter group (Figure 1).

Mean level of plasma aldosterone in patients with heart transplants was not different from that in the control group: 0.50 ± 0.48 vs 0.40 ± 0.25 nmol/liter, respectively (p = NS, after logarithmic transformation). Plasma aldosterone in the control group showed a significant nocturnal decrease (p <0.01), resembling the familiar profile of plasma cortisol (not shown). The profile of patients appeared rather like a reflected image of the normal profile (Figure 2). The variability, however, did not reach statistical significance.

Cortisol was not detected in patients. Plasma prednisolone, as expected, showed 2 peaks around 8 A.M. and 8 P.M., corresponding to the times of administration of the drug.

Mean transverse level of atrial natriuretic factor was much higher in patients than in control subjects: 93.0 ± 56.7 vs 20.7 ± 8.9 pg/ml, respectively, p <0.001. A subtle but significant elevation around midnight (p <0.05) was seen in control subjects, whereas a circadian variation was not observed in patients (Figure 3). Mean levels of atrial natriuretic factor in patients did not correlate with pulmonary wedge or right atrial pressures, p >0.1. There was no correlation with plasma renin activity in either patients or controls.

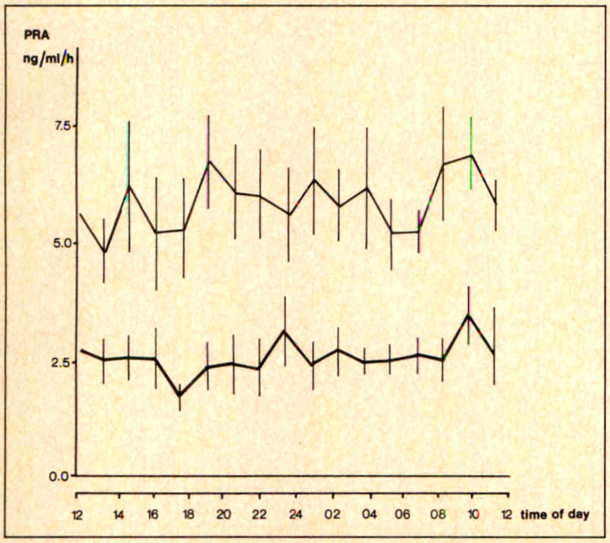

FIGURE 1. Plasma renin activity (PRA) during 24-hour supine rest in 10 cardiac transplant recipients *(upper curve)* and in 10 age-matched control subjects *(lower curve)*. Values are mean ± SEM.

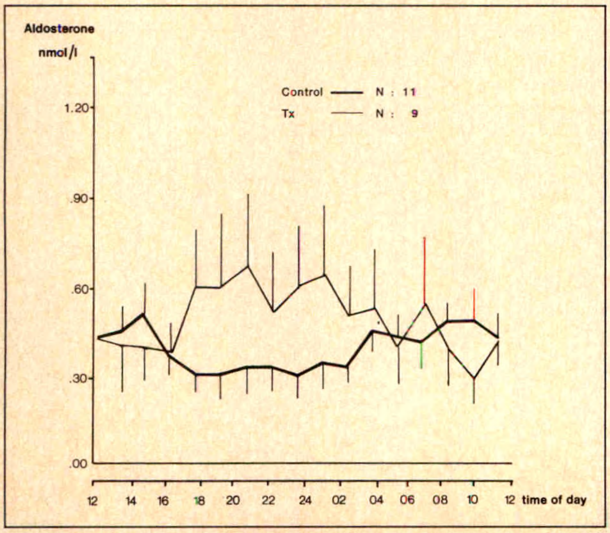

FIGURE 2. Plasma aldosterone during 24-hour supine rest in cardiac transplant recipients (Tx) and in age-matched control subjects. Values are mean ± SEM.

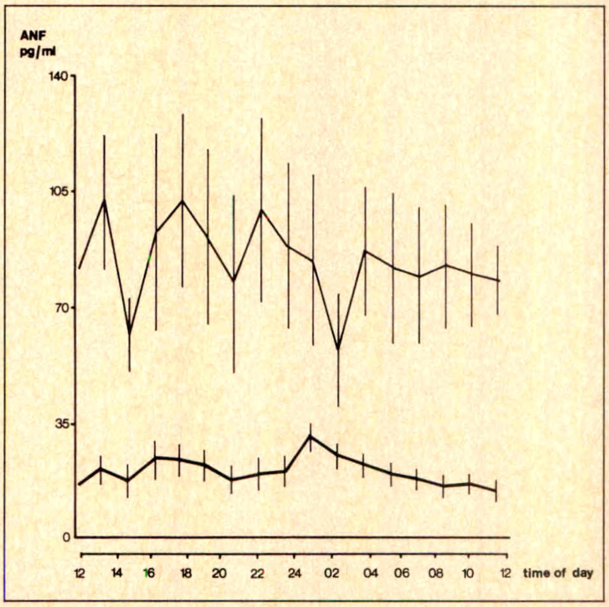

FIGURE 3. Plasma atrial natriuretic factor (ANF) during 24-hour supine rest in 10 cardiac transplant recipients *(upper curve)* and in 12 age-matched control subjects *(lower curve)*. Values are mean ± SEM.

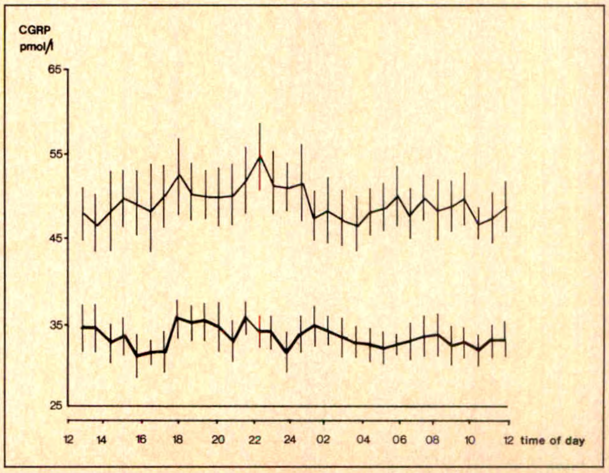

FIGURE 4. Serum calcitonin gene-related peptide (CGRP) during 24-hour supine rest in 10 cardiac transplant recipients *(upper curve)* and in 12 age-matched control subjects *(lower curve)*. Values are mean ± SEM.

Pancreatic polypeptide showed a highly significant diurnal variability in both patients and controls ($p < 0.001$). Mean levels in patients were only insignificantly lower than levels in the control group (34.2 ± 34.7 vs 50.7 ± 32 pmol/liter, respectively [p = NS] after logarithmic transformation).

Since initial screening had shown measurable levels of neuropeptide Y in only one third of the samples, a complete set of blood samples from only 4 patients/controls were analyzed. In these series, levels above the detection limit of 20 pmol/liter were found in only 34% of the samples. Mean level in patients, however (31.5 pmol/liter, range 25 to 50), was not different from the mean level of controls (28.3 pmol/liter, range 23 to 40).

Calcitonin gene-related peptide was higher in patients than in control subjects (49.7 ± 9.9 vs 33.3 ± 5.7 pmol/liter, respectively, $p < 0.01$) and showed a significant circadian variation ($p < 0.05$) with a decrease during the hours from midnight until noon. In control subjects, a significant diurnal variation was not found (Figure 4).

The influence of the postoperative time span on various parameters was evaluated through a breakdown of patient data: half of the patients (group I) who underwent transplantation <6 months before the study (mean 3.8 + 2.1 months) were compared with the other half (group II) who had transplantation >6 months previously (22.2 ± 12.6 months). In group II a tendency for reappearance of a nocturnal decrease in systolic but not diastolic pressure was seen (Figures 5 and 6). The 24-hour heart rate profile was normal in both groups (Figure 7). The difference in mean levels was not significant.

Only minor variations between the 2 groups were seen in the various hormones measured. However, mean value for pancreatic polypeptide was much lower in group II (12.6 ± 11.3 pmol/liter) than in group I (51.6 ± 37.3 pmol/liter ($p < 0.05$); the normally pronounced

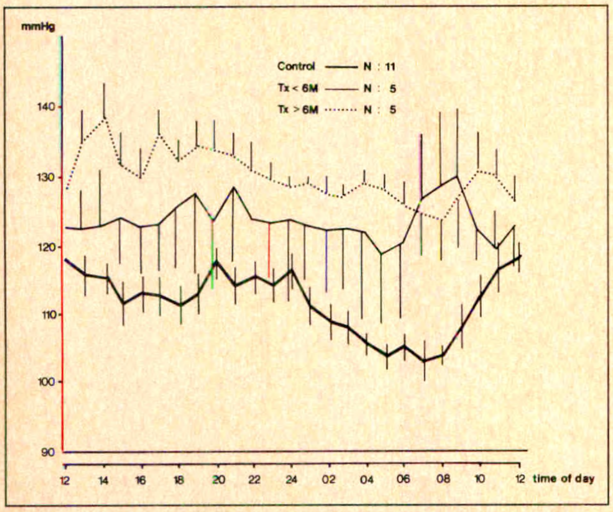

FIGURE 5. Systolic blood pressures during 24-hour supine rest in cardiac transplant recipients studied >6 (Tx >6 M) and <6 (Tx <6 M) months postoperatively, and in age-matched control subjects. Values are mean ± SEM.

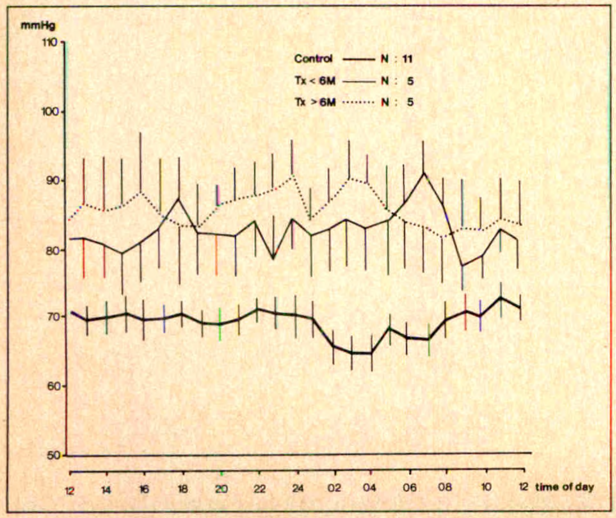

FIGURE 6. Diastolic blood pressures during 24-hour supine rest in cardiac transplant recipients studied >6 (Tx >6 M) and <6 (Tx <6 M) months postoperatively, and in age-matched control subjects. Values are mean ± SEM.

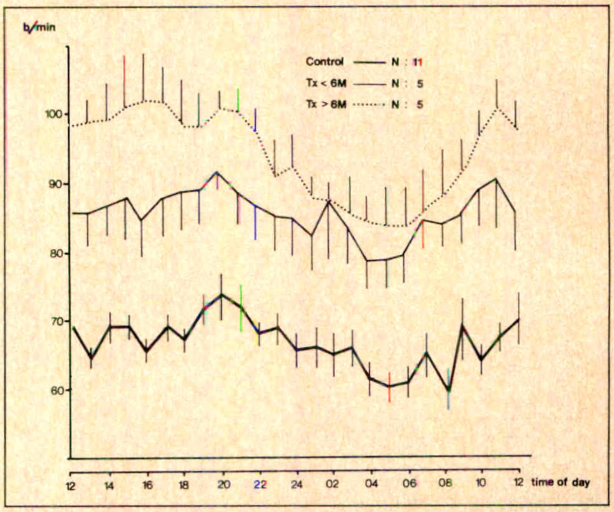

FIGURE 7. Heart rates (b/min) during 24-hour supine rest in cardiac transplant recipients studied >6 (Tx >6 M) and <6 (Tx <6 M) months postoperatively, and in age-matched control subjects. Values are mean ± SEM.

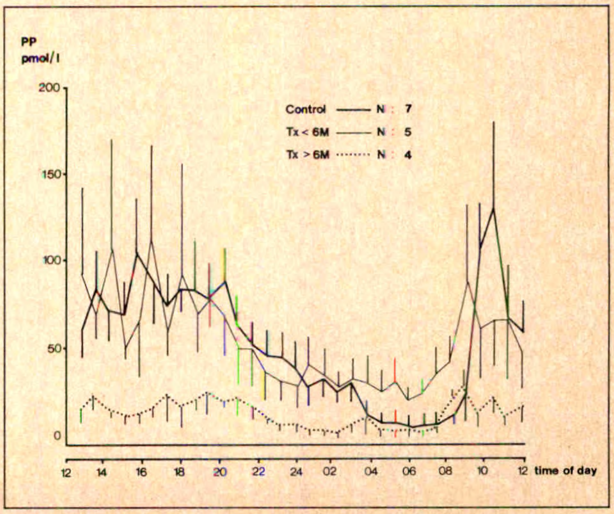

FIGURE 8. Plasma pancreatic polypeptide (PP) during 24-hour supine rest in cardiac transplant recipients studied >6 (Tx >6 M) and <6 (Tx <6 M) months postoperatively, and in age-matched control subjects. Values are mean ± SEM.

oscillations, also seen in group I, had nearly disappeared in patients with a longer transplant status (Figure 8). In contrast, noradrenaline was remarkably stable, showing a completely normal profile and level in both groups of patients with heart transplants (Figure 9).

There was no difference in serum creatinine between the 2 subgroups: 1.11 ± 0.2 vs 1.18 ± 0.3 mg/dl (p = NS). There was also no difference in age: 42.5 ± 10.1 vs 32.6 ± 9.2 years (p = NS); group I vs group II, respectively.

There was no difference in length of sleep between patients and controls, and both groups slept between midnight and 7 P.M.

DISCUSSION

The lack of a normal circadian blood pressure profile but preserved (though often blunted) nocturnal decrease in heart rate appears to be a consistent finding in patients who have undergone cardiac transplantation.[2,10] A common explanation of the absent nocturnal decline in blood pressure refers to the shift in blood volume from the periphery to a more central location during recumbency. This, together with the force-fed pump characteristics of the denervated heart, counteracts the blood pressure–lowering effect of a diminished nocturnal sympathetic drive to the blood vessels.[1,2] Although such a mechanism may play a role in patients studied during ambulation, as in previous investigations, it does not suffice in explaining the loss of a nocturnal pressure decrease in our patients studied during 24-hour recumbency to avoid major shifts in blood volume due to changes in position.

The assumption that a preserved nocturnal heart rate decrease in patients with heart transplants is related to a decline in circulating catecholamines[2] has been confirmed by the present investigation. Plasma noradrenaline in these patients showed both normal mean levels and 24-hour variability, irrespective of the length of the postoperative follow-up period.

In the majority of blood samples for plasma adrenaline and neuropeptide Y, and in all samples for dopamine, levels were below the detection limits in both patients and controls, thus making the construction of 24-hour profiles impossible. However, measurable levels of adrenaline and neuropeptide Y did not differ between the 2 groups.

The circadian variability in pancreatic polypeptide in our patients with <6 months follow-up closely resembles that of the control group and those of other studies.[11] The lower levels and severely blunted 24-hour profile in patients studied more than half a year after transplantation might thus suggest a possible, progressive parasympathetic neuropathy. Thus, impaired secretion of pancreatic polypeptide has also been shown in patients with diabetic autonomic neuropathy[12] and chronic autonomic failure.[13] Alternatively, because pancreatic polypeptide cells are located in the pancreas including the islets,[14] the cyclosporine-induced pancreatic damage suggested by a number of studies in both the experimental animal[15] and in humans[16] might interfere with secretion, causing the blunted response observed in patients studied late postoperatively.

Contrary to other studies in cyclosporine-treated cardiac transplanted patients showing unstimulated renin levels,[17,18] the transverse mean level of plasma renin activity in our patients was slightly above the upper limit of 4.3 ng/ml/hour and significantly higher than in the control group, even when the 3 patients receiving antihypertensive medication are excluded (5.9 ± 1.7 vs 2.6 ± 0.4 ng/ml/hour, $p < 0.01$, patients vs controls, respectively). The suggestion that the short- and long-term effects of cyclosporine on the renin-aldosterone system differ[19] might explain these discrepancies. The mean time interval from transplantation to study was thus shorter in the present study than in the majority of previously reported studies and renal function was better as indicated by a lower serum creatinine level.

We did not find a significant 24-hour variability in plasma renin activity either in patients or in controls. Although significant diurnal variations in normal subjects have been reported, this does not appear to be a consistent finding.[20]

In accordance with another series,[17] we found normal levels of aldosterone in cardiac transplanted patients. The abnormal diurnal profile of aldosterone in our patients is most likely caused by the administration of steroids which all patients received. Also a seemingly reversed aldosterone profile, as suggested in the present study, has been noted by others[20] after suppression of adrenocorticotropic hormone.

The significantly elevated level of atrial natriuretic factor in our patients is consistent with other studies in heart transplanted patients.[18,21,22] A diurnal variability was not found in patients, contrary to the significant circadian variation seen in the control group.

The lack of correlation between right atrial pressure and the mean transverse level of atrial natriuretic factor in our study supports earlier reports showing no correlation between these 2 parameters[22] or between atrial size and plasma atrial natriuretic factor.[18] Obviously, release mechanisms additional to atrial pressure and stress are at work, the latter according to Laplace's law being increased 12% by the one-fourth increase in atrial size after heart transplantation.[21] These mechanisms might

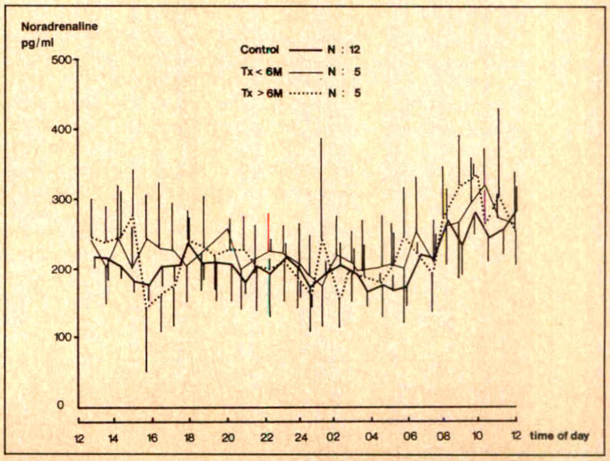

FIGURE 9. Plasma noradrenaline during 24-hour supine rest in cardiac transplant recipients studied >6 (Tx >6 M) and <6 (Tx <6 M) months postoperatively, and in age-matched control subjects. Values are mean ± SEM.

include the recently described chronotropic[23] and calcitonin gene-related peptide-induced[24] stimulation of atrial natriuretic factor, both of which were elevated in our patients.

Calcitonin gene-related peptide is a novel peptide described as the most powerful vasodilator yet discovered.[25] Both in the experimental animal[26] and in humans,[27] the peptide further produces tachycardia in the absence of any changes in blood pressure. Thus, apart from the lack of parasympathetic tone and the augmented adrenergic sensitivity of the transplanted heart[28] the significantly elevated levels in our patients may well play a role in their increased heart rate. The significant decrease in calcitonin gene-related peptide during late evening — coincident with the decrease in heart rate — may further support variations in noradrenaline to maintain a circadian rhythmicity in heart rate in cardiac transplanted patients. Finally, the recently reported stimulation of renin by calcitonin gene-related peptide[29] may be involved in the elevation of plasma renin activity found in our patients.

In conclusion, this study has probably raised more questions than given answers. We have provided an explanation for the increased heart rate and preserved diurnal rhythmicity in heart transplanted patients. With findings of a modest increase in renin opposing very high levels of atrial natriuretic factor and elevated levels of the powerful vasodilator calcitonin gene-related peptide, we have no explanation for the abnormalities in blood pressure. Finally, although a recent study has shown increased sympathetic nerve firing in cyclosporine-treated cardiac transplant recipients,[30] the results of the present study indicate that basal sympathetic 24-hour rhythmicity is preserved. All other hormonal systems studied have shown abnormalities either in level or circadian variability, or both.

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Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
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Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $< 5\%$ cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricen
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References: 1. IMS National Prescription Audit (NPA), August 1991. Compared with year-to-date August 1991 percentage growth in new prescriptions among the 10 leadi
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Rate-Corrected Mean Velocity of Fiber Shortening–Stress at Peak Systole as a Load-Independent Measure of Contractility

George G. S. Sandor, MB, ChB, FRCP(C), Ruby Popov, RN, Eustace De Souza, BSc, RDCS, RDMS, Starr Morris, RDMS, and Beverley Johnston, RDCS

The relation of mean velocity of fiber shortening–stress at end-systole is a good load-independent index of left ventricular contractility, but involves simultaneous M-mode echocardiography, carotid tracing and blood pressure determination, which may be impractical in children. As stress at peak systole and end-systole are closely related, this study examined whether the relation of mean velocity of fiber shortening–stress at peak systole could be used as a simpler method of assessing left ventricular contractility in a normal population of children. In addition, the cross-sectional normal range for a pediatric population was obtained. In 25 normal children aged 4 to 17 years (mean age 11), rate-corrected mean velocity of fiber shortening ($MVCF_c$), stress at peak systole (σPS), and end-systolic stress (σES) were determined using echocardiography, carotid pulse tracing and blood pressure measurement. Six patients with cardiomyopathy (mean age 8 years) were also studied. The relation of stress at peak systole and end-systolic stress was $\sigma PS = 1.004\ \sigma ES + 12.0$ ($r = 0.91$, $SEE = 4.98$; $p < 0.001$) for the normal group, and $\sigma PS = 1.083\ \sigma ES + 7.7$ ($r = 0.99$, $SEE = 4.07$; $p < .001$) for the cardiomyopathic group. This slope of the regression line was slightly higher and the difference was statistically significant. The slope of $MVCF_c = 0.0066\ \sigma PS + 1.55$ ($SEE = 0.131$, $r = -0.52$) was nearly identical to that of $MVCF_c = 0.0065\ \sigma ES + 1.46$, ($SEE = 0.135$, $r = -0.46$), with no difference in the regression coefficients. Individual measurements for the cardiomyopathic group fell on similar parts of the graph whether stress at peak systole or end-systole was used for the ordinate of the plot with $MVCF_c$.

Thus, in the absence of outflow obstruction, the relation of $MVCF_c$–stress at peak systole correlates well with the relation using stress at end-systole and can be used to assess left ventricular contractility.

(Am J Cardiol 1992;69:403–407)

The development of the end-systolic wall stress–velocity of fiber shortening relation by Colan et al[1] produced an echocardiographic load-independent measure of cardiac function. The technique involves simultaneous M-mode echocardiography, blood pressure measurement and carotid pulse tracings. Previous studies[2–6] established that the carotid pulse tracing contour and the position of the dicrotic notch closely resemble the central aortic pressure contour, enabling the calculation of pressure and stress at end-systole. Colan et al derived a cross-sectional normal range for adults, some of whom were challenged with preload, afterload or inotropes. A recent report by Franklin et al[7] established a pediatric cross-sectional normal range.

Carotid pulse tracings may be technically difficult to obtain in some children, and need additional manpower and hardware that is not readily available on echocardiographic equipment. Because some invasive hemodynamic and echocardiographic studies[8–11] showed a close relation between peak systolic and end-systolic pressures and stress, this study was performed to examine whether this was true for the noninvasively derived stress at peak systole–fiber shortening and end-systolic stress–fiber shortening relations. This study was also performed to confirm the pediatric cross-sectional normal range for the latter.

METHODS

The study protocol was approved by the University of British Columbia clinical research committee and also by the British Columbia's Children's Hospital research committee.

Echocardiography: Studies were performed with the children in a quiet, resting, unsedated state. The technique of M-mode echocardiography was standard.[12] With the patient lying supine in a right anterior oblique position, an ultrasound image of the midleft ventricle was obtained with a 3 or 5 MHz transducer using an Advanced Technology Laboratories mark 600 echocardiographic machine. When the midleft ventricular position was obtained, M-mode echocardiography was performed with a simultaneous carotid pulse tracing using the Cambridge Pulse Transducer system connected to the ultrasound machine. When satisfactory waveforms were obtained, they were recorded on the same tracing at a paper speed of 50 mm/second. With the blood pressure cuff already in place, blood pressure was immediately obtained without moving the child. Systolic time intervals were obtained by echocardiography in the standard manner.

From the Division of Cardiology, Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada. This study was supported by Hospital for Sick Children Foundation, Toronto, Ontario, and The Heart and Stroke Foundation of British Columbia and Yukon, Vancouver. Manuscript received July 2, 1991; revised manuscript received September 26, 1991, and accepted September 29.

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TABLE I Clinical Details of the Two Groups

	Control Subjects	p Value	Patients*
No. of pts.	25		6
No. of echoes	50		15
Age (yr)			
Mean	11	0.29	8
Range	4–17		4–6
Rate-controlled mean velocity of fiber shortening (mean ± SD)	1.1 ± 0.15	<0.001	0.74 ± 0.22
Stress at peak systole (mean ± SD)	63.3 ± 12	<0.001	110 ± 3
Stress at end-systole (mean ± SD)	51 ± 11	<0.001	95 ± 29

*Indicates first echocardiogram only.

Patients: Twenty-five children aged 4 to 17 years (mean 11) with normal clinical cardiac examinations were studied twice within 2 months and constituted the control group (group 1).

Six patients who presented with cardiac failure due to a variety of causes were studied on >1 occasion and constituted group 2. The causes of cardiac failure were viral cardiomyopathy (1 patient), idiopathic dilated cardiomyopathy (1), anthracycline therapy (2), and 2 patients presented with renal failure (1 due to hemolytic uremic syndrome and the other due to Wegener's granulomatosis).

Calculations: The methods of determining end-systolic pressure from carotid pulse tracing and blood pressure were standard. The distances between the peak and diastolic carotid pulse tracing (Y) and also the dicrotic notch (X) were measured and assigned the values of the systolic and diastolic blood pressures. The distance to the dicrotic notch from diastole on the carotid pulse tracing was proportional to the difference of end-systolic from diastolic pressure (Figure 1). Thus, end-systolic pressure was calculated as: ESP = (X/Y) (pulse pressure) + (diastolic blood pressure). Stress at end-systole was calculated from[13]: $\sigma ES = ESP \cdot LVES \cdot 1.35/4$ $PWS\ (1 + PWS/LVES)$, where σES = stress at end-systole, ESP = pressure at end-systole (mm Hg), LVES = LV dimension at end-systole (cm), and PWS = posterior wall thickness at systole (cm). Stress at peak systole was calculated from: $\sigma PS = PSP \cdot LVES \cdot 1.35/4$ $PWS\ (1 + PWS/LVES)$, where σPS = stress at peak systole and PSP = pressure at peak systole. Mean velocity of fiber shortening (MVCF) was calculated from: MVCF = LVED − LVES/LVED × ET, where LVED = left ventricular end-diastolic dimension (cm), and ET = ejection time (seconds), and was rate-corrected ($MVCF_c$) by $ET/\sqrt{R\text{-}R}$. Thus: $MVCF_c = LVED - LVES/LVED \times (ET/\sqrt{R\text{-}R})$.

Statistics: Group comparisons were analyzed by standard parametric unpaired *t* tests with Bonferroni correction. Relations of end-systolic stress, and stresses at peak systole and $MVCF_c$ and systolic stress were analyzed by linear regression analysis. Regression coefficients (slopes) were tested by *t* test of significance.

RESULTS

The mean values for shortening fraction, $MVCF_c$–stress at peak and end-systole for the control subjects (group 1) and from the first echocardiograms obtained from the patients (group 2) are listed in Table I.

The relation of stress at end-systole and peak systole is very close (Figure 2A) ($\sigma PS = 1.004\ \sigma ES + 12.0$, $r = 0.91$, SEE 4.98, $p < 0.001$, for the control group). The plot of $MVCF_c$ for both stress at peak systole and end-systolic stress with confidence limits is shown in Figure 3. The mean slope of $MVCF_c = -0.0066\ \sigma PS + 1.55$ (SEE 0.131, $r = -0.52$) is virtually identical to that of $MVCF_c = -0.0065\ \sigma ES + 1.46$ (SEE 0.135, $r = -0.46$), with no difference in regression coefficients ($p = 0.97$).

The relation of stress at end-systole and peak systole for group 2 (Figure 2B) is very close also ($\sigma PS = 1.083\ \sigma ES + 7.7$ [SEE = 4.07, $r = 0.99$, $p < 0.001$]). The slope is slightly higher than that for control subjects (group 1), and the difference is statistically significant.

Figure 4 shows the individual plots of group 2 studies for the 2 methods and demonstrates a very similar picture, using either stress at peak systole or end-systole. The asterisks indicate the first echocardiographic study

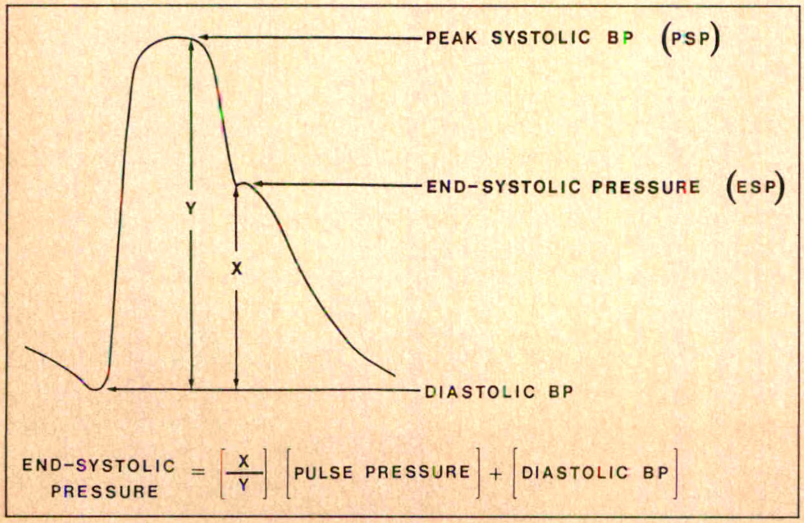
PEAK SYSTOLIC BP (PSP)
END-SYSTOLIC PRESSURE (ESP)
Y
X
DIASTOLIC BP
END-SYSTOLIC PRESSURE = [X/Y] [PULSE PRESSURE] + [DIASTOLIC BP]

FIGURE 1. Diagram of carotid pulse tracing indicating method of calculating end-systolic pressure based on Colan et al.[4] BP = blood pressure.

performed in each patient. Although the points on the graph are not numbered, each point for stress at end-systole corresponds very closely to that for stress at peak systole.

DISCUSSION

The normal values for ejection phase indexes (i.e., ejection fraction, $MVCF_c$ and stress at peak and end-systole) for the control group were similar to the results of Colan et al[1] and Franklin et al,[7] confirming uniformity of technique. The slope and intercepts of the $MVCF_c$–end-systolic stress relation also closely resemble the slopes determined by Colan and Franklin and their respective coworkers, with wider 95% confidence limits than Colan et al, but a very similar range to that reported by Franklin et al. This may be due to a different age range of our control group compared with that of Colan et al's or to a smaller number of patients. Thus, the techniques used in these studies were shown to be reproducible in pediatric patients.

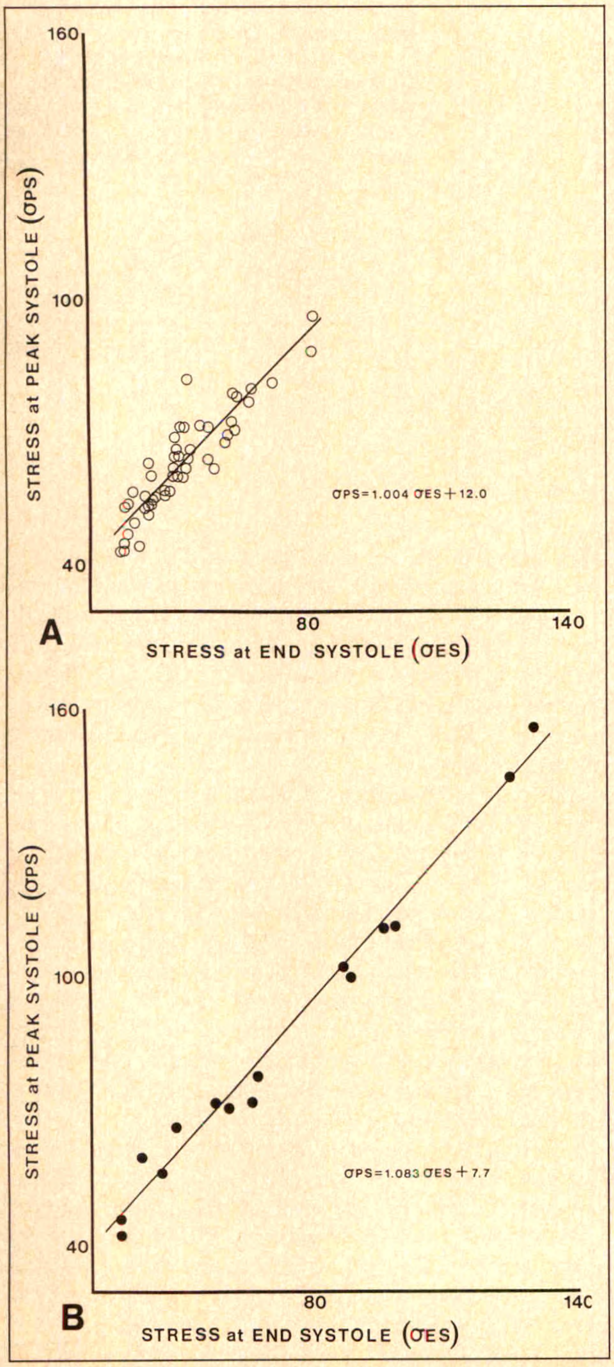

FIGURE 2. ***A,* relation of stress at peak systole and end-systole for the normal group ($\sigma PS = 1.004\ \sigma ES + 12.0$, r = 0.91, SEE = 4.98, $p < 0.001$, 50 echocardiograms). *B,* relation of stress at peak systole and end-systole for cardiomyopathy group ($\sigma PS = 1.083\ \sigma PS + 7.7$, r = 0.99, SEE = 4.07, $p < 0.001$, 15 echocardiograms).**

In establishing the noninvasive method of determining stress at end-systole there were a number of catheterization studies that demonstrated a close resemblance between carotid pulse[3–6] and central aortic tracing. In the unobstructed left ventricle, several investigators noted the close relation of peak-systolic to end-systolic pressure, and consequently, that of stress at peak systole and end-systole, which is usually approximately 10% lower.[8,10,11] These stresses were calculated using angiographic or echocardiographic measurements of left ventricular systolic dimension and wall thickness. Some investigators also used peak systolic pressure or stress for assessing cardiac function in conjunction with radionuclear studies, echocardiography, or both.[9–11]

There are practical difficulties in performing simultaneous blood pressure reading, carotid pulse tracing and echocardiography in children, and most echocardiographic machines do not have carotid pulse modules, and some cannot be adapted to have them. Conditions such as aortic regurgitation may pose difficulties in determining the position of the dicrotic notch, and the use of peak systole would be more practical. The close relation of stress at peak systole and end-systolic stress needed to be explored in the context of the $MVCF_c$ relation. The nearly identical mean slopes and bounds of the $MVCF_c$–stress at peak systole and $MVCF_c$–end-systolic stress in the control subjects (group 1) may therefore have been expected. The higher intercept represents the higher value for peak pressure or stress. Figure 4 shows that for the patients (group 2), the methods

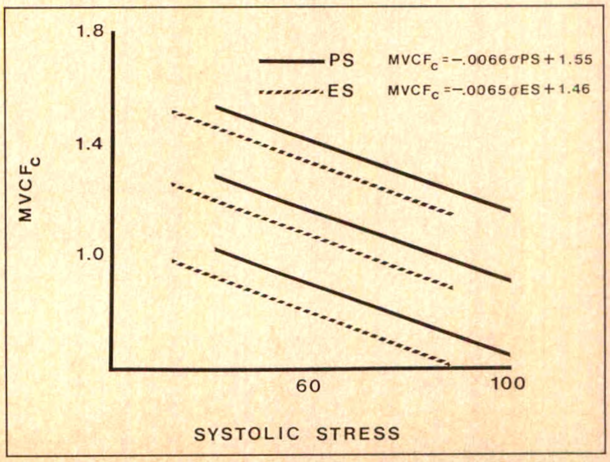

FIGURE 3. Plot of rate-corrected mean velocity of fiber shortening ($MVCF_c$) and stress at peak systole (PS) *(solid lines)* or end-systole (ES) *(dashed lines)* with mean slope and 95% confidence limits for both.

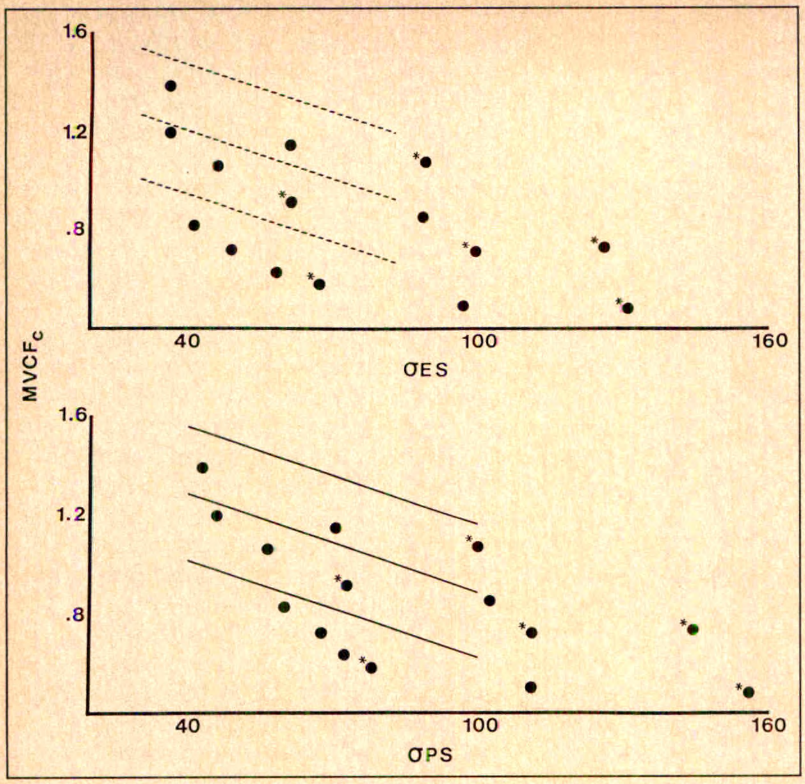

FIGURE 4. Plots of individual values for cardiomyopathic group on normal ranges for both methods demonstrating nearly identical positions for each value and denoting first echocardiogram. σES = stress at end-systole; MVCF$_c$ = rate-corrected mean velocity of fiber shortening; σPS = stress at peak systole.

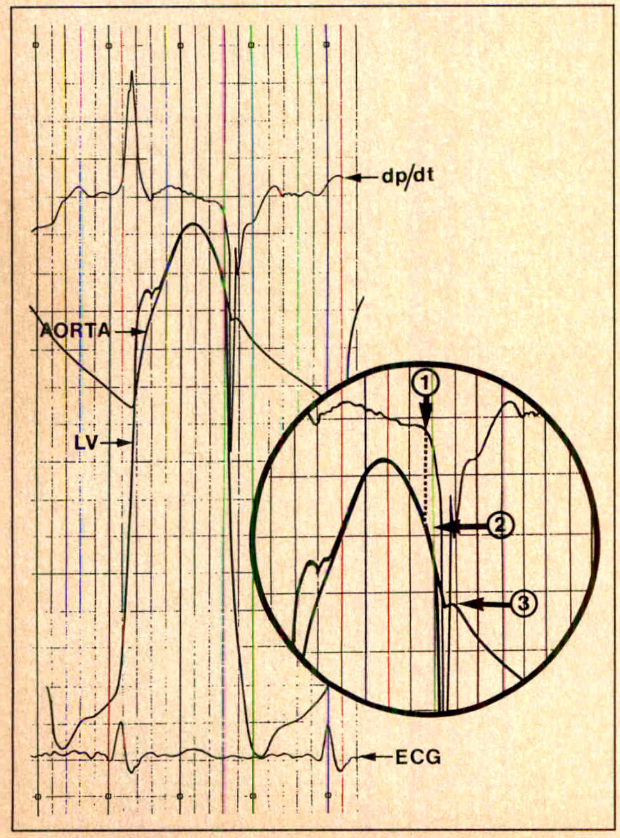

FIGURE 5. High-fidelity left ventricular (LV) pressure tracing, with first derivative of left ventricular pressure (dp/dt) and aortic pressure tracing superimposed. *Upper arrow (1)* depicts onset of mechanical relaxation at onset of rapid negative deflection of dp/dt, and *lower arrows (2)* depict pressure at that time and *(3)* pressure at dicrotic notch. This is enlarged to show detail more clearly. ECG = electrocardiogram.

were interchangeable. Each point was in virtually the same area of the graph for either method, and no patient who had normal contractile function by end-systolic stress was categorized incorrectly using stress at peak systole, and vice versa. This occurred despite a different relation of stress at peak systole and end-systolic stress in group 2. However, this did not affect the assessment of contractility.

There are theoretical considerations that need to be examined. In previous echocardiographic studies, stress at end-systole was taken to mean stress at end-ejection (i.e., when the aortic valve closes, as indicated by the dicrotic notch or by echocardiographic aortic valve closure.[1,7] This point in time does not, in fact, signify mechanical end-systole (i.e., the end of isobaric contraction just before ventricular relaxation). Figure 5 shows a high-fidelity left ventricular pressure tracing with the first derivative of left ventricular pressure, and, superimposed on it, the aortic pressure trace on withdrawal in a normal patient obtained during an unrelated hemodynamic study. At the point when the rapid negative deflection begins in the first derative of left ventricular pressure tracing (i.e., the onset of relaxation), the ventricular pressure is 7 to 8 mm Hg higher than that at which the aortic dicrotic notch occurs. This period of time between true end-systole and the closure of the aortic valve was named by Barath and Antaloczy[14] as the "auxobaric relaxation period," during which left ventricular pressure decreases. Thus, mechanical end-systole is temporally not the same as end-systole, indicated by end-ejection, and has a higher pressure, and peak systolic pressure is closer to true end-systole than was previously estimated using end-ejection as end-systole. Colan et al[15] in an elegant study of patients with renal failure plotted left ventricular pressure dimension curves from the onset of aortic valve opening to closing. They clearly showed that the pressure/dimension curve sloped downward after the peak pressure/dimension value due to the reduction in left ventricular pressure until the aortic valve closed. Thus, Colan et al[15] also showed that the pressure at left ventricular mechanical end-systole is higher than that at the time of aortic valve closure.

There are limitations to this technique that are common to all echocardiographic measurements of end-systole. Because the septal maximal contraction[12] occurs before peak posterior wall contraction, it is not clear which point represents end-systole. By convention, left ventricular end-systolic diameter is measured at peak septal contraction, but the posterior wall thickness (obtained at maximal thickening) occurs slightly later. This may not correlate with the timing of peak systole.

Thus, theoretical and technical assumptions were used in the calculation of the standard $MVCF_c$–end-systolic stress relation. Our study also makes some assumptions, but represents a practical, simpler alternative method that gives similar information. Unlike Colan et al,[1] this study did not alter loading conditions, and such a study should be performed. The increased slope of stress at peak systole/end-systolic stress for group 2 may indicate that this relation does not remain constant in patients with myocardial dysfunction and needs to be established with altered loading conditions and inotropes, although this would pose practical and ethical problems. There is no evidence to suggest that the difference would be of practical significance, as shown by the similarity of the 2 graphs in Figure 3. Descriptions of the use of these indexes for long-term follow-up of patients with thalassemia[16] or receiving anthracycline[17] medication have already appeared in the literature, but to date, variability studies have not been performed and are also clearly needed. The bounds of individual variability may be less than the cross-sectional normal range, and for follow-up studies, these techniques may be even more sensitive than would be indicated by the use of the normal range shown here.

The ability of the $MVCF_c$–end-systolic stress relation (and hence, the $MVCF_c$–stress at peak systole relation) to adequately detect myocardial dysfunction was questioned by Roman et al,[18] who suggested that artifactual normalization of these indexes may occur by taking preload and heart rate into account. The purpose of this study was not to validate the theoretical aspects of the test, but to demonstrate the similarity of stress at peak systole to that at end-systole.

This study confirmed the cross-sectional normal range for the $MVCF_c$–end-systolic stress relation in a group of pediatric patients. In the absence of outflow obstruction, the $MVCF_c$–stress at peak systole relation is a simpler and more practical method of assessing load-independent contractility.

Acknowledgment: Thanks are due to Cathy Cordoni for the typing and preparation of the manuscript.

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Prevalence and Predictors of Ventricular Premature Complexes in Survivors of Acute Myocardial Infarction

Stuart J. Connolly, MD, and John A. Cairns, MD, on behalf of the CAMIAT Pilot Study Group*

The presence of ventricular premature complexes (VPCs) on ambulatory electrocardiographic monitoring early after acute myocardial infarction (AMI) has been shown to independently predict subsequent all-cause mortality and sudden death.[1–16] The hypothesis that antiarrhythmic drug therapy might reduce mortality in patients identified to be at high risk of sudden death continues to attract attention to postinfarction ventricular arrhythmias. The prevalence of any VPCs on 24-hour electrocardiographic recording has varied in previous reports from 65 to 95%.[4,7–16] Previous studies evaluating the prevalence of ventricular arrhythmia in survivors of AMI have not been population-based. Cohort studies that analyze only a subset of all patients with the disease of interest in a geographic area will be susceptible to bias unless the cohort is selected in a systematic way to eliminate bias. In previous studies the method of patient accrual has often not been explicitly stated, and where it has been, the selection process has excluded specific subsets of the source population or has depended heavily on referral. In such non-population–based studies, referral patterns may lead to a patient sample that is unrepresentative of the source population. In addition, the degree of use of β blockers and antiarrhythmic drugs has been unclear in many previous studies. This study was undertaken to determine the incidence of and predictors of ventricular arrhythmia on the ambulatory electrocardiogram among all hospitalized survivors of AMI occurring in a defined geographic area over a 1-year period.

This study was conducted in the 5 coronary care units of Hamilton, Ontario (population 390,000 in 1986), where the general policy is to admit every patient with possible AMI without age restriction. From May 12, 1986, until May 11, 1987, a nurse practitioner visited each of the coronary care units on a daily basis to document every admission and to assign the diagnosis of AMI when the patient had ≥2 of the following: (*1*) *characteristic ischemic pain in the precordium or associated referral areas lasting ≥15 minutes after the patient was at physical and emotional rest;* (*2*) *elevation of ≥2 of aspartate aminotransferase, creatine kinase or lactate dehydrogenase to greater than twice the upper limit of normal for the given hospital, or creatine kinase MB fraction to >5% of the total creatine kinase;* (*3*) *development of new 40 ms Q waves in ≥2 adjacent electrocardiographic leads or development of dominant R waves in lead V_1 or development of evidence of non-Q-wave infarction (ST depression ≥1 mm or T-wave inversion ≥3 mm in ≥2 adjacent electrocardiogram leads, lasting at least 7 days);* (*4*) *death in hospital within 2 hours with any 1 of these criteria positive. The following were not included in the analysis:* (*1*) *patients with out-of-hospital cardiac arrest;* (*2*) *patients transferred to a Hamilton hospital from other hospitals outside of the community;* (*3*) *patients readmitted to the coronary care unit with a second myocardial infarction during the same admission as their first myocardial infarction. Patients who survived ≥5 days after coronary care unit admission and who were discharged alive from the coronary care unit became eligible for 24-hour ambulatory electrocardiographic monitoring, which was performed between 6 and 30 days after the onset of acute AMI between 0900 and 1700 hours. The tape was analyzed only if there was ≥18 hours of electrocardiographic recording free of major artifact. Ventricular tachycardia was defined as ≥3 VPCs with an RR interval of <600 ms. The ambulatory electrocardiographic analysis system was validated against annotated American Heart Association tapes with accuracy >95%. Because the duration of recording varied among tapes, results were normalized to a 24-hour period of recording. When the patient was receiving an antiarrhythmic drug, if the patient's physician agreed, the drug was temporarily discontinued ≥5 drug half-lives before the recording.*

Patients were dichotomized according to whether the ambulatory electrocardiogram showed ≥240 VPCs/24 hours, and a stepwise multivariate discriminant function analysis was performed to determine which variables best discriminated the 2 groups. The following variables were included in this analysis: age, sex, peak creatine kinase, non-Q-wave infarction, anterior infarction, heart rate in emergency room, ventricular fibrillation during

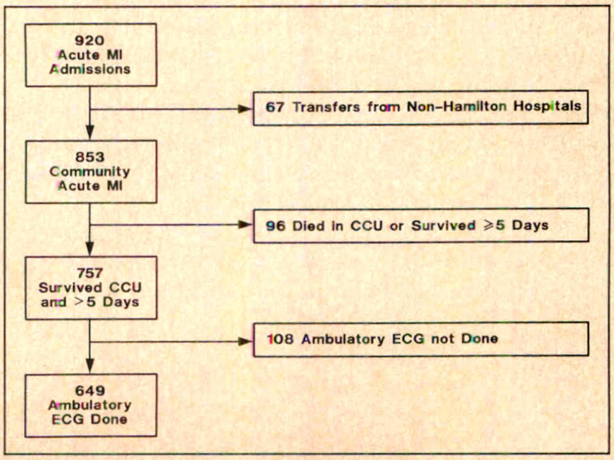
920
Acute MI
Admissions
67 Transfers from Non–Hamilton Hospitals
853
Community
Acute MI
96 Died in CCU or Survived ⩾5 Days
757
Survived CCU
and >5 Days
108 Ambulatory ECG not Done
649
Ambulatory
ECG Done

FIGURE 1. Flow diagram showing how the patient cohort was assembled. CCU = coronary care unit; ECG = electrocardiogram; MI = myocardial infarction.

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*See Appendix.

AMI, prior AMI, heart failure during AMI, shock during AMI, bradycardia arrest during AMI, digoxin therapy, and β blocker therapy.

From May 12, 1986, until May 11, 1987, 920 admissions to the Hamilton coronary care units were assigned a final diagnosis of AMI, including 34 patients with 2 AMIs during the year. Sixty-seven of these patients were transferred from outside of the Hamilton community and were excluded from subsequent analysis. Of the remaining 853 patients with AMI, 96 (11.3%) died before discharge from the coronary care unit or within 5 days of admission. Thus, 757 patients were eligible for 24-hour ambulatory electrocardiographic monitoring by the study criteria. A 24-hour electrocardiogram was performed on 649 of these patients (85.7%). Figure 1 is a flow diagram showing how the patient study population was assembled. The failure to perform the ambulatory electrocardiogram was most often the result of early patient discharge or severity of patient illness. Mean time of the ambulatory electrocardiogram was 10 ± 12 days after admission to the hospital for AMI, and 89% were performed within 14 days of admission.

Patient clinical characteristics are listed in Table I. Only 6% of patients were receiving antiarrhythmic drug therapy; of those, most (71%) were receiving a Vaughan-Williams Class 1A drug. Table II shows the results of the ambulatory electrocardiographic recording. VPCs were present in 80.4% of patients, ≥72 VPCs/24 hours were present in 29.4%, and ≥240 VPCs/24 hours were present in 19.4%. Ventricular tachycardia occurred in 8% of patients, <1% had >10 runs in 24 hours. Among patients with ventricular tachycardia, in 50% the longest run was only 3 beats in duration; in only 4% was the longest run >10 beats in duration. Couplets were present in 21.6% of patients; only 3.7% of patients had ≥24 couplets/24 hours.

The results of the multivariate stepwise discriminant function analysis are listed in Table III. The only variables that were statistically significant independent predictors of an ambulatory electrocardiogram with ≥240 VPCs/24 hours were congestive heart failure, previous AMI and age. The presence of congestive heart failure, previous AMI and age >65 years can be used to predict the likelihood of a patient having ≥240 VPCs/24 hours on ambulatory electrocardiogram. Each of the 647 patients for whom these data were available was scored as having from none to 3 of these criteria positive. Table III shows the relation between the number of positive criteria and the presence or absence of ≥240 VPCs/24 hours on ambulatory electrocardiogram. In 224 patients (34.6%), none of the 3 criteria was positive and only 6.3% of those patients had ≥240 VPCs/24 hours. In the 186 patients with 2 or 3 positive criteria, 39.2% of patients had ≥240 VPCs/24 hours. To look at it in another way, if only patients with ≥2 positive criteria were subjected to ambulatory electrocardiographic monitoring, 73 of the 125 (58.4%) positive ambulatory electrocardiograms would have been recorded, at a cost of performing ambulatory electrocardiography in only 186 of the 647 patients (28.7%). The relation between sensitivity and specificity (receiver-operator curve) for prediction of ≥240 ventricular premature depolarizations/24 hours for 1, 2 and 3 positive criteria is shown in Figure 2.

TABLE I Patient Clinical Characteristics (n = 649)

Mean age (years)	64 ± 13
Men/women	457 (70%)/192 (30%)
Peak CK (U/liter)	1,280 ± 1,294
Anterior myocardial infarction	286 (44%)
Ventricular fibrillation during AMI	31 (5%)
First heart rate (beats/min)	82 ± 22
Previous AMI	193 (30%)
Shock during AMI	36 (6%)
CHF during AMI	140 (22%)
β-blocker therapy	173 (27%)
Digitalis therapy	109 (17%)
Calcium antagonist therapy	330 (60%)
Antiarrhythmic drug therapy	37 (6%)

AMI = acute myocardial infarction; CHF = congestive heart failure; CK = creatine kinase.

This study included almost completely patients in this community surviving the coronary care unit stay for AMI. The ambulatory electrocardiogram was not recorded in 14.3% of potentially eligible patients, but this was because of the severity of the patient's illness in 40% of these patients. Drug therapy during the ambulatory electrocardiogram has been carefully described. Only 27% of patients were receiving a β blocker. Although β blockers can reduce VPC frequency, β blocker therapy was not an independent predictor of low VPC frequency in this study. Calcium antagonists were given more often but these drugs have little effect on VPC frequency. Antiarrhythmic drug therapy was taken during the ambulato-

TABLE II Ambulatory Electrocardiographic Results (n = 649)

VPCs			Couplets			Runs		
No. of VPCs	Pts. (%)	Cumulative (%)	No. of Couplets	Pts. (%)	Cumulative (%)	No. of Runs	Pts. (%)	Cumulative (%)
0	19.6	19.6	0	78.4	78.4	0	92.0	92.0
1–11	33.4	53.0	1–11	15.3	93.7	1–5	6.3	98.3
12–23	7.9	60.9	12–23	2.3	96.0	6–9	0.6	98.9
24–71	9.7	70.6	24–47	1.7	97.7	≥10	1.1	100.0
72–143	6.3	76.3	≥48	2.3	100.0			
144–239	4.3	80.6						
240–719	7.4	88.0						
720–1,439	4.4	92.4						
≥1,440	7.6	100.0						

VPCs = ventricular premature complexes.

TABLE III Relation of Congestive Heart Failure, Previous AMI and Age >65 Years to Presence of ≥240 VPCs/24 Hours

No. of Criteria Positive	Total Pts.	Pts. (%) with <240 VPCs/24 Hours	Pts. (%) with ≥240 VPCs/24 Hours
0	224	210 (93.7)	14 (6.3)
1	237	199 (84.0)	38 (16.0)
2 or 3	186	113 (60.8)	73 (39.2)
Total	647	522 (80.7)	125 (19.3)

AMI = acute myocardial infarction; VPCs = ventricular premature complexes.

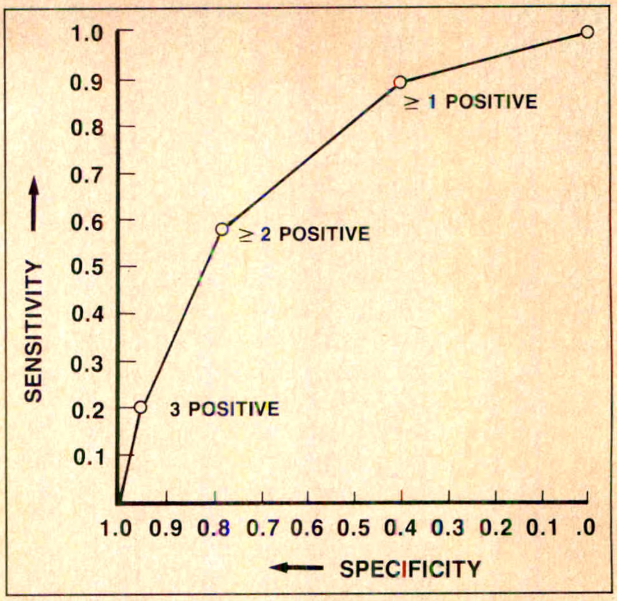

FIGURE 2. The relation of sensitivity to specificity for prediction of ≥240 ventricular premature depolarizations/24 hours using the 3 criteria of congestive heart failure, previous myocardial infarction and age >65 years.

ry electrocardiogram in only 6% of patients. Comparison of these results with previous studies is difficult because previous studies have used recording durations ranging from 1 to 24 hours, and the methods of expressing VPC frequency and the presence of repetitive VPCs have varied from study to study. Use of classification systems were quite common; they tended to group together different types of ventricular arrhythmia. For example, the results of Ruberman et al,[11] who used the term "complex arrhythmia" which includes frequent, multiform or repetitive, cannot be easily compared with the results of other studies that used either the Lown classification or other classification scheme. The incidence of any VPC on a 24-hour recording has varied from 65 to 95% in previous reports.[4,7–16] The 2 largest and most recent studies are those of the Multicentre Postinfarction Research Group (819 patients)[15] and of Kostis et al (3,290 patients).[16] The reported incidence of any VPC on 24-hour recording was 86 and 84%, respectively, slightly higher than the 80% incidence of the present study. Ten or more VPCs/hour were present in 14 and 13% of patients in these studies and in 20% in the present study. The incidence of a least 1 ventricular tachycardia run has varied, on 24-hour recordings, from 1.6 to 19.5%. In the study of the Multicentre Postinfarction Research Group the incidence of ventricular tachycardia was 11.2%, similar to the 8.2% incidence in the present study.

Only Kostis et al,[16] using placebo patients from the β Blocker Heart Attack Trial, previously analyzed predictors of high-risk ventricular arrhythmia in survivors of AMI. They reported that age, prior myocardial infarction and congestive heart failure were the only independent predictors of high-risk ventricular activity among 11 variables in a multivariate stepwise linear regression analysis. With use of a somewhat different set of 13 variables and a multivariate discriminant function analysis, the present study has found that the same 3 variables were the only independent predictors of frequent VPCs. When these 3 variables are used as 3 dichotomous criteria, the post-AMI population can be classified into 3 groups.

One group is low risk and has only a 6.3% chance of having a 24-hour recording with ≥240 VPCs/24 hours, whereas the high-risk group has a 39.2% chance, a 6.2-fold difference. Table III could be used to decide in which post-AMI patients ambulatory electrocardiography is to be performed. For example, if an effective treatment was known to benefit patients with ≥240 VPCs/24 hours, one might choose to record the ambulatory electrocardiogram on all patients or perhaps patients with 1 or more positive criteria in order to reduce the risk of missing a patient who could benefit from treatment. On the other hand, if one were screening for identification of patients with high-risk VPCs for potential entry into a randomized trial, one might choose to record the ambulatory electrocardiogram only in patients with ≥2 positive criteria in order to conserve resources.

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APPENDIX

Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) pilot study group: Ernest Fallen, MD, McMaster University Medical Centre; Lorne Finkelstein, MD, Chedoke Hospital; Stuart J. Connolly, MD, Hamilton General Hospital; Paul H. Tanser, MD, St. Joseph's Hospital; Brian J. Sealey, MD, Henderson General Hospital; and John A. Cairns, MD, Hamilton General Hospital.

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Consequences of a Media Campaign Focusing on Delay in Acute Myocardial Infarction

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The early phase of acute myocardial infarction is particularly critical. The majority of deaths occur outside the hospital, mainly due to ventricular fibrillation.[1] Furthermore, it has been convincingly shown that early intervention with β blockers[2,3] and particularly thrombolysis[4,5] can limit infarct size and improve prognosis. Therefore, a media campaign was performed in Göteborg, Sweden, during 1 year, with the intention of reducing delay times and increasing use of the ambulance for patients suspected of having acute myocardial infarction (AMI).

A team consisting of 1 nurse, 3 doctors and a copywriter with specific interest in advertising was responsible for planning, conducting and evaluating the campaign. The planning took place during a 6-month period. During this time, the budget was planned. We estimated that the campaign would cost approximately 400,000 U.S. dollars. Money was collected mainly during the planning phase by funds and support from the industry (mainly pharmaceutical). The message of the campaign, developed by physicians and nurses on the team, was: for chest pain lasting >15 minutes dial immediately 90 000 for ambulance transport to the hospital, because the pain may indicate AMI. A slogan developed by the copywriter was used: HEART–PAIN–90 000. In Sweden it translates as HJÄRTA–SMÄRTA–90 000, which has a more emotional and rhythmic sound, evocative of popular song texts. Only 1 message was used, and it was thought that this message could reach both the young and the elderly. The message was spread mainly by printed material. Television was not used.

The campaign took place in Göteborg, a city with 450,000 inhabitants. A nurse was responsible for the conduction of the campaign and worked full-time on it during the initial phase. The campaign began in November 1987 with a 3-week intensive phase. During this time, all available media, with the exception of household-distributed leaflets, were simultaneously used. The intensive phase was followed by a maintenance phase.

Only 1 radio station (the local one for Göteborg) was involved. Articles on AMI were written in the main local Göteborg newspaper at 4-month intervals, but advertisements in the newspaper appeared more often. The departments of medicine in the 2 city hospitals took active part in the campaign. Thus, all patients admitted to the coronary care unit were given a leaflet in which not only the Heart–Pain–90 000 message was included, but also a careful description of symptoms of AMI and of the possibilities of early intervention. This leaflet was available to patients in various parts of the department of medicine, including the postinfarction clinic. The same leaflet was also distributed to all local district clinics in the city where doctors responsible for the campaign made on-site visits and explained the rationale behind the campaign. The leaflet was also distributed to all households in Göteborg twice (100,000 on each occasion).

Advertisements on buses and trams were in place continuously during various months of the campaign.

Between February 15, 1986, and December 31, 1988 (i.e., 21 months before and 13 months after the beginning of the campaign), all patients admitted to the emergency room of Sahlgrenska Hospital were prospectively evaluated in terms of initial degree of suspicion of AMI based on clinical history and initial electrocardiographic pattern. Before the beginning of the campaign, the clinical course among all patients with chest pain was carefully evaluated during 1-year follow-up. During the campaign, the clinical course of patients with AMI was evaluated during initial hospitalization, as well as mortality during 1-year follow-up. Infarct size was estimated from the highest recorded activity of serum aspartate aminotransferase (ASAT) and creatine kinase. Serum activity of ASAT was determined once daily during the first 3

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TABLE I Previous History Among Patients with Acute Myocardial Infarction Before and During Campaign

	Before Campaign, n = 921 (%)	During Campaign, n = 632 (%)	p Value*
Acute myocardial infarction	30	32	
Angina pectoris	51	42	<0.001
Congestive heart failure	21	13	<0.001
Systemic hypertension	36	29	<0.01
Diabetes mellitus	12	12	
Age (mean ± SEM; yr)	70.0 ± 0.4	71.6 ± 0.4	<0.01

*p values denoted if $p < 0.05$.

days in the hospital and of creatine kinase 12 and 20 hours after onset of symptoms. Mortality during 1-year follow-up was determined according to the Swedish National Registry of Deaths.

AMI was diagnosed if patients met 2 of the following 3 criteria: (1) chest pain ≥15 minutes, (2) ≥2 values of ASAT above the normal range, and (3) appearance of new Q waves in a 12-lead standard electrocardiogram.

Pitman's nonparametric test was used. A p value <0.05 was regarded as significant. Results are expressed as percent values, mean ± standard error of the mean and median.

During the 21-month period before the campaign, 921 patients with AMI were admitted to Sahlgrenska Hospital through the emergency room compared with 632 during the year of the campaign. The median delay time was reduced from 3 hours before to 2 hours and 20 minutes (p <0.001) during the campaign. In Table I, the 2 infarct populations are described in terms of clinical history. Some differences were observed. Patients with AMI before the campaign were younger, but more often appeared to have a history of angina pectoris, hypertension and congestive heart failure.

As shown in Table II, the percentage of patients arriving in the hospital within various time periods after

TABLE II Percentage of Patients with Acute Myocardial Infarction Arriving in the Hospital Within Various Time Limits With and Without Simultaneous Consideration of the Initial Electrocardiogram

	Before Campaign, n = 908 (%)	During Campaign, n = 536 (%)	p Value*
Delay (hours)†			
≤3	50	57	<0.01
≤6	67	74	<0.01
≤12	80	89	<0.001
≤24	88	96	<0.001
Delay (hours) and ST elevation‡			
≤3	22	29	<0.01
≤6	30	36	<0.05
≤12	34	39	
≤24	37	42	<0.05

*p values denoted if $p < 0.05$.
†Percentage of all patients with acute myocardial infarction arriving in hospital within various time intervals after onset of pain; ‡percentage of all patients with acute myocardial infarction arriving in hospital within various time intervals after onset of pain and showing ST elevation in electrocardiogram on admission.

TABLE III Mortality Among Patients with Acute Myocardial Infarction Before and During Campaign

	Before Campaign, % (n)	During Campaign, % (n)
In-hospital mortality		
All patients	14 (919)	13 (632)
Patients <75 years	10 (555)	9 (352)
All CCU patients	13 (777)	11 (529)
CCU patients <75 years	8 (513)	8 (323)
One-year mortality		
All patients	29 (905)	28 (632)
Patients <75 years	19 (546)	18 (352)
All CCU patients	26 (766)	25 (529)
CCU patients <75 years	17 (505)	18 (323)

CCU = coronary care unit.

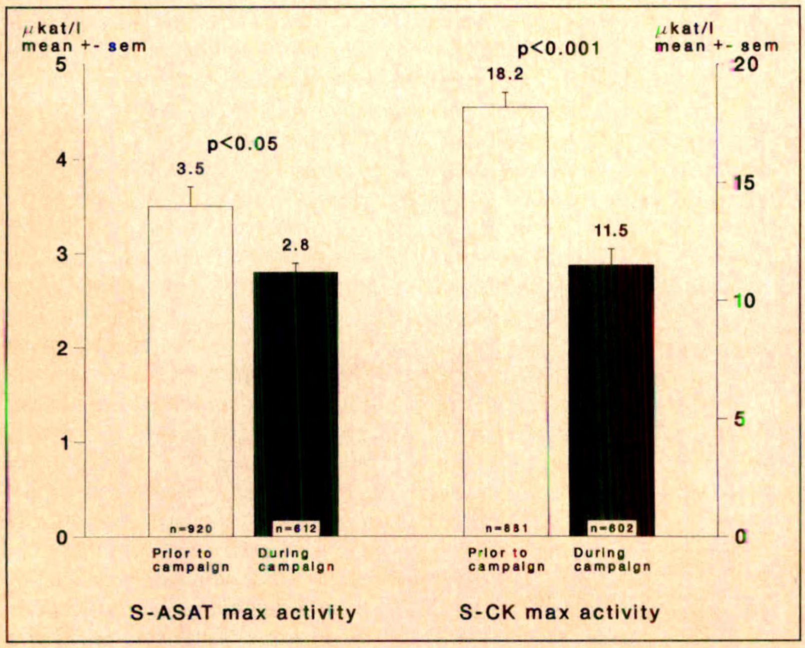

FIGURE 1. Estimated infarct size according to maximal (max) serum enzyme activity before and during campaign. S-ASAT = serum aspartate aminotransferase. S-CK = serum creatine kinase.

onset of pain were increased during the campaign. When applying both the criteria for delay time and ST-segment elevation it was shown that the percentage of patients with AMI with delay time ≤ 6 hours and ST elevation on admission increased from 30% before to 36% during the campaign ($p < 0.05$). The percentage of patients who actually received thrombolysis was only 4% before and 13% during the campaign.

As shown in Table III, mortality did not significantly change during the campaign compared with that during 21 months before its beginning.

As shown in Figure 1, estimated infarct size was significantly reduced during the campaign compared with that during 21 months before its beginning. The duration of hospitalization was 11 ± 0.3 days before and 12 ± 1 days during the campaign ($p > 0.2$).

The percentage of patients who developed ventricular fibrillation before arrival in the hospital, in the emergency room and coronary care unit or another ward was lower during the campaign compared with that of the period before the campaign (8.7% before vs 5.9% during the campaign; $p < 0.05$). Among patients who developed ventricular fibrillation before arrival in the hospital or emergency room, or <4 hours after arrival in the coronary care unit during the campaign ($n = 28$), 73% stated that they were aware of the campaign, and one third of these patients stated that they were influenced to go quicker to the hospital by the message.

As previously reported,[6,7] the impact of the campaign in the emergency department was impressive during the first week when the number of patients with chest pain and no suspicion of AMI increased from 4 to 14 daily. This large increase rapidly declined thereafter.

A media campaign aimed at reducing delay time in AMI significantly increased eligibility for early thrombolysis due to a shortened delay time. Possibly as a consequence of this, infarct size appeared to be reduced, although mortality was not affected.

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Interobserver Variability in Grading of Coronary Arterial Narrowings Using the American College of Cardiology/American Heart Association Grading Criteria

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The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Assessment for Diagnostic and Therapeutic Cardiovascular Procedures guidelines for the grading of coronary arterial lesions were devised to predict the potential difficulty of revascularizing vessels with such lesions and to assess the potential complication rate when percutaneous transluminal angioplasty or other percutaneous procedures are used.[1] This grading system has rapidly gained wide acceptance and is frequently used to design studies, to report results and, potentially, to compare the outcomes of different percutaneous transluminal angioplasty operators. The grading system consists of several components each of which is subject to variable interpretation. Therefore, we undertook this study to determine the degree of interobserver variability incurred in using this system.

One hundred fifty cineangiograms of consecutive percutaneous transluminal coronary angioplasty procedures were selected. All films were reviewed independently by 2 experienced (>500 cases) angioplasty operators who had worked together extensively for 4 years. Cine runs used for grading consisted of all views obtained before insertion of guidewires or balloon catheters. Lesion length was assessed using the diameter of the guiding catheter. The 2 reviewers were unaware of the outcomes (both clinical and angiographic) of the procedures. Angiograms were reviewed for all category components of the grading system. Thrombus was defined as a convex border of a complete obstruction or an intraluminal lucency surrounded on ≥ 3 sides by contrast. Clinical history was not used for this analysis; therefore, chronicity of total occlusion was judged, based on presence or absence of intraluminal staining and absence of runoff branches immediately proximal to the lesion, which indicated recent occlusion, or on presence of bridge collaterals, which suggested chronic occlusion.

The number of vessels diseased in each patient was graded using the Coronary Artery Surgery Study system.[2] Angiographic success was defined as reduction of percent diameter stenosis to $<50\%$ with no complications occurring.

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TABLE I Interobserver Agreement by Lesion Grade

	A	B	C	Total
A	19	27	0	46
B	8	64	17	89
C	1	9	5	15
	28	100	22	150

Interobserver variability for each characteristic was expressed as the fraction of the total number of narrowings for which both observers agreed. Variability between the 2 observers was also expressed using the kappa coefficient (k),[3] where k = (observed agreement − chance agreement)/(1 − chance agreement).

The average age of the patients was 60 ± 13 years. Ninety-seven patients (65%) were men. Previous myocardial infarction was present in 45 patients (30%), and 16 (10%) had prior coronary artery bypass surgery, whereas 44 (30%) had prior coronary angioplasty. One-vessel disease was present in 64 patients (43%), 2-vessel in 45 patients (30%), and 3-vessel in 31 patients (21%). Angiographically successful dilatation occurred in all patients, except 5 who underwent emergency bypass surgery, although 32 (22%) were hospitalized overnight in the coronary care unit for heparin or nitroglycerin infusion, or both.

Interobserver agreement for the 3 grades was only 61% ($k = 0.244$): for A versus non-A lesions it was 79% ($k = 0.446$), and for C versus non-C lesions it was 81% ($k = 0.181$). Agreement for all 3 lesion types is shown in Table I. For each characteristic, agreement was: occlusion 95% ($k = 0.375$), ostial location 95% ($k = 0.200$), thrombus 95% ($k = 0$), calcification 88% ($k = 0.375$), branch jeopardy 87% ($k = 0.353$), contour irregularity 80% ($k = 0.461$), angulation 75% ($k = 0.294$), eccentricity 72% ($k = 0.425$), length 66% ($k = 0.247$), and accessibility 61% ($k = 0$). Total agreement for all categories was present for only 18 films (12%). Examples of disagreements are shown in Figures 1 to 3.

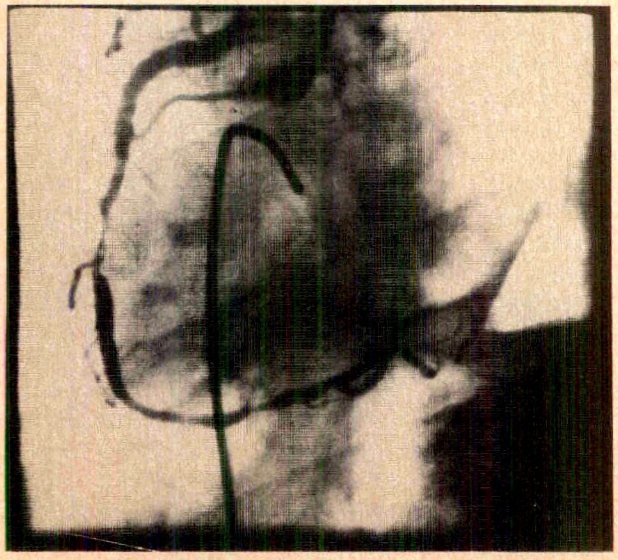

FIGURE 1. Right coronary arterial lesion graded C by observer 1 and B by observer 2. Disagreement on length, angulation, calcification, and presence of thrombus.

Previous reports documented interobserver variability with regard to the grading of coronary angiograms for degree of narrowing[4] and for Thrombolysis in Myocardial Infarction flow grade.[5] Our study shows that interobserver variability in grading lesions using the ACC/AHA criteria is equally high. Two very experienced observers who had worked together extensively were intentionally selected to minimize disagreement. Even so, the rate of discordance was surprising. Agreement was best with regard to presence of chronic total occlusion, and worst with regard to accessibility. Importantly, lesion length (a prime determinant of type C grading) was associated with poor agreement. This may be a consequence of the measurement of narrowing length in centimeters, which requires calibration according to catheter diameter. Such calibration is often used for angiographic analysis of vessel luminal diameter, which is generally between 1 and 1.5 catheter diameters; however, the measurement of lesion length (which may be >7 catheter diameters) would

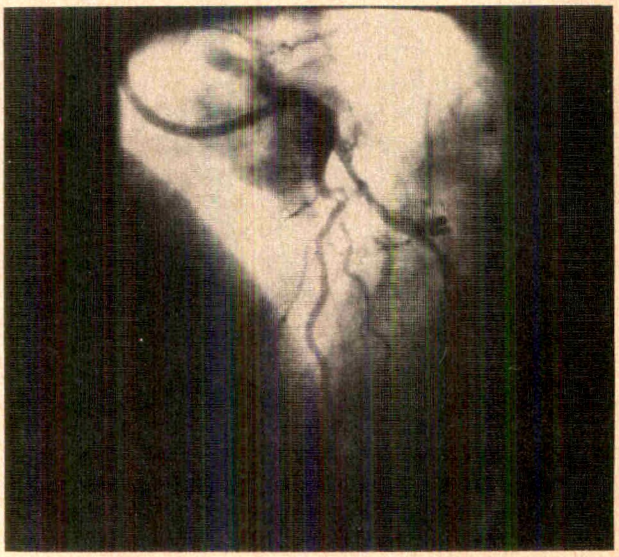

FIGURE 2. Left anterior descending coronary arterial lesion graded by both observers. Disagreement on angulation, ulceration, and eccentricity.

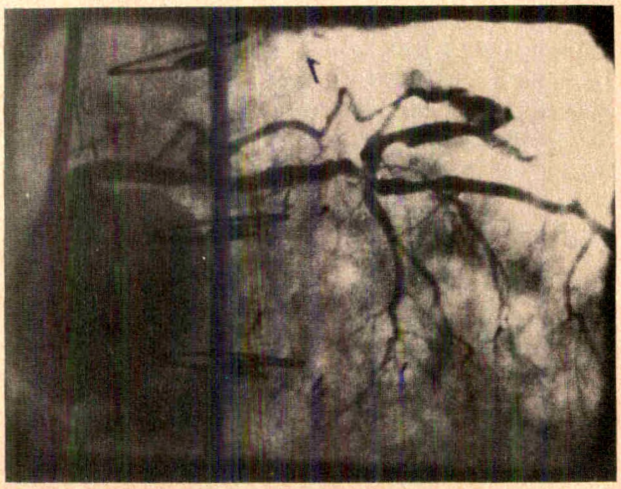

FIGURE 3. Left anterior descending coronary arterial lesion graded C by observer 1 and B by observer 2. Disagreement on angulation, calcification, accessibility, eccentricity, and ease of protecting branch points.

magnify calibration errors several fold more. Although several studies reported on angiographic characteristics of lesions likely to predict poor angiographic and clinical outcome following percutaneous transluminal coronary angioplasty,[6-12] the individual characteristics found to predict acute closure or ischemic complications varied from study to study. These differences may be consequences of differing definitions of lesional characteristics and outcomes, of varying interpretations of individual cineangiograms, or merely of multiple comparisons.

Agreement rates among observers for the characteristics studied were reported in 2 studies, but in a smaller number of patients. The group at Emory University found 5 angiographic characteristics to predict the occurrence of ischemic complications, and although this report preceded the ACC/AHA guidelines, 3 characteristics form part of the current criteria.[7] Rates of discordance in 40 patients were reported to be 22% for lesion length (expressed as a proportion of the vascular diameter), 20% for branch point stenosis, and 24% for lesion eccentricity.[7] Since promulgation of the guidelines, the Multiple Vessel Angioplasty Prognosis Study Group reported intraobserver variability among 57 stenoses in 25 patients. Minor modifications in the ACC/AHA guidelines were used, and category B lesions were subdivided into categories B1 and B2, depending on the presence of ≥1 group B characteristic. Complete agreement was present in 58% of cases, and disagreement by 2 classification units (1 ACC/AHA grade) occurred in 7%.[10] Although the discordance exceeds that in our study, our use of 3 rather than 4 grades would be expected to increase concordance, and the smaller number of lesions compared in that study would lead to wider confidence intervals.

Grading according to the ACC/AHA guidelines has proven useful for predicting clinical outcomes following percutaneous transluminal coronary angioplasty.[10] However, our data imply that caution should be used when applying these criteria to comparisons between operators or institutions. Perhaps even more important, a host of new technologies and antithrombotic agents now promise to limit the complication rates for percutaneous revascularization of high-risk lesions. Our findings underscore the absolute need to evaluate these modalities in randomized clinical studies.

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Lack of Correlation Between the Signal-Averaged Electrocardiogram and Regional Wall Motion Abnormalities in Coronary Artery Disease

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Late potentials on the signal-averaged electrocardiogram (SAECG) are believed to reflect slow-impulse conduction in areas of abnormal myocardium,[1] and have been shown to be a sensitive marker for spontaneous or inducible ventricular tachycardia (VT).[2,3] However, late potentials also occur in some patients without VT, thus limiting the specificity of signal-averaging in prospectively identifying patients destined to develop this arrhythmia. Because the presence of myocardial scar might alter electrical conduction and produce a late potential on the SAECG even without VT, we hypothesized that regional left ventricular (LV) dysfunction in patients with coronary artery disease would increase the likelihood of an abnormal SAECG, and thus at least partially account for its nonspecificity for VT.

Signal-averaged electrocardiography was performed in 156 patients with no history of VT and no symptoms suggestive of sustained tachyarrhythmia, who underwent diagnostic cardiac catheterization and coronary angiography at our institution between October 1989 and

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TABLE I Clinical Characteristics of Study Groups and Results of Signal-Averaged Electrocardiography

	Age (yr)	EF (%)	Total QRS (ms)	LAS (ms)	RMS 40 (μV)
Controls (n = 36)	57 ± 10	70 ± 8	96 ± 9	32 ± 9	41 ± 31
Group 1 (n = 42)	59 ± 12	67 ± 8	97 ± 12	30 ± 9	51 ± 44
Group 2 (n = 43)	59 ± 11	53 ± 10	98 ± 12	29 ± 9	51 ± 45
Group 3 (n = 35)	60 ± 13	42 ± 12	101 ± 13	34 ± 12	40 ± 36

Values are mean ± standard deviation for each group.
EF = ejection fraction; LAS = low-amplitude signal, $<40\ \mu V$; RMS 40 = root-mean-square voltage of terminal 40 ms; Total QRS = total filtered QRS duration.

December 1990. This included 120 patients with significant coronary artery disease (defined as >70% luminal narrowing of at least 1 epicardial coronary artery), and a control group of 36 patients with normal coronary arteries and normal LV function who underwent cardiac catheterization to evaluate chest pain. Patients with concomitant valvular or myocardial disease other than prior myocardial infarction were excluded from the study, as were those with bundle branch block on the surface electrocardiogram.

SAECGs were obtained with a model 1200 EPX high-resolution electrocardiograph (Arrhythmia Research Technology). The vector magnitude of X, Y and Z leads was determined and filtered with a bidirectional Butterworth filter at 40 to 250 Hz. Approximately 200 beats were averaged to achieve a noise level $<0.5\ \mu V$ *in each case. The duration of the filtered QRS (total QRS), duration of the low-amplitude signal* $<40\ \mu V$*, and root-mean-square voltage of the terminal 40 ms were calculated by computer and visually inspected. The values were classified as normal or abnormal according to 2 different sets of published criteria.*[2,3]

The biplane left ventriculograms were reviewed by 2 observers unaware of the results of the SAECG. The patients with coronary artery disease were divided into 3 groups on the basis of the most severe wall motion abnormality present: group 1, normal LV wall motion; group 2, regional hypokinesia; and group 3, regional akinesia or dyskinesia. The mean values for each parameter of the SAECG were then calculated for the control and coronary disease groups, and the percentages of patients in each group who had abnormalities of individual signal-averaged electrocardiographic parameters were also determined. Statistical differences in the results of signal averaging between groups were sought with t testing.

The clinical characteristics of the 4 study groups are listed in Table I. Mean ages of the groups did not differ, and not unexpectedly, ejection fraction decreased significantly with increasing severity of wall motion abnormality ($p = 0.001$ *for groups 2 vs 1, and for groups 3 vs 2). Mean values for total QRS, low-amplitude signal* $<40\ \mu V$*, and terminal root-mean-square voltage for each of the 4 groups are also listed in Table I. There were no statistically significant differences in these values between the control group and any of the 3 coronary disease groups.*

Table II shows in each patient group how often the individual signal-averaged electrocardiographic parameters were abnormal, and how often at least 1, 2 or all 3 parameters were abnormal, using the reference values of Gomes et al.[2] *According to these criteria, an abnormal total QRS was unusual in any group, but abnormalities of the low-amplitude signal* $<40\ \mu V$*, terminal root-mean-square voltage, or both, were nearly equally common in all 4 groups. At least 1 signal-averaged electrocardiographic parameter was abnormal in 31% of the control patients, and ≥2 parameters were abnormal in 25%. Similar percentages of abnormal parameters were also found in each of the 3 coronary disease groups.*

The results of the same analysis were only slightly different when the normal reference values of Caref et al[3] *were substituted, which are somewhat less restrictive for total QRS and somewhat more restrictive for the low-amplitude signal* $<40\ \mu V$ *and terminal root-mean-square voltage. According to these criteria, patients in groups 2 and 3 were significantly more likely to have abnormal total QRS than control patients. However, there were no significant differences between any groups in the incidence of an abnormal low-amplitude signal or terminal root-mean-square voltage, or in the frequency of an abnormal SAECG by 1 or 2 criteria.*

TABLE II Frequency of Abnormal Parameters of the Signal-Averaged Electrocardiogram in Study Groups

	Total QRS (>114 ms)	LAS (>38 ms)	RMS 40 (<20 μV)	No. of Abnormal Parameters ≥1	≥2	3
Controls	3	28	28	31	25	3
Group 1	5	19	29	31	21	0
Group 2	9	14	17	21	14	5
Group 3	6	31	34	34	29	6

Values shown are percentages of patients in each group with the corresponding abnormal result. None of the differences between groups is statistically significant.
Abbreviations as in Table I.

This study did not demonstrate an independent influence of regional LV dysfunction on the SAECG. The presence of abnormal wall motion from prior myocardial infarction did not significantly alter the mean value of any signal-averaged electrocardiographic parameter relative to a control group of patients with normal coronary arteries and LV function. The likelihood of an abnormal SAECG by 1 or 2 parameters was surprisingly high in the control group, but was not substantially higher in any of the groups with coronary disease. These findings confirm the nonspecificity of the SAECG for VT, and suggest that regional LV dysfunction is not responsible for this nonspecificity.

Our results differ from those of Breithardt et al,[4] who detected late potentials in only 9% of patients with normal wall motion compared with 46% of patients with regional akinesia or dyskinesia. However, the recording methodology and semiqualitative criteria for diagnosing late potentials in their study differed markedly from those currently used by most investigators[2,3] and used in our report. In addition, the results differ primarily in the higher frequency of late potentials recorded in our control group, which also exceeds the frequency of an abnormal SAECG in normal subjects reported previously in several other studies.[2,5,6] However, our "normal" patients had undergone cardiac catheterization and were much older than the normal subjects in those studies, which consisted of nurses and medical residents[2] or other healthy volunteers who had not undergone cardiac catheterization.[5,6] Increasing age has been found recently to independently increase the incidence of late potentials,[7] and probably accounts for the frequency of late potentials in our control group. This finding of a reduced positive predictive value of the SAECG in older patients has important implications for the prospective value of this test, because the question of susceptibility to VT is far more likely to be raised in older patients with suspected heart disease than it is in young, healthy people.

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Efficacy and Safety of a New Selective Class III Antiarrhythmic Agent Dofetilide in Paroxysmal Atrial Fibrillation or Atrial Flutter

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The acute treatment of patients with paroxysmal atrial fibrillation (AF) and atrial flutter (AFl) has gained new interest recently. Although direct-current cardioversion is frequently used if oral loading with quinidine is unsuccessful, there is increasing evidence that class IC antiarrhythmic agents, when used intravenously, are extremely effective for conversion of paroxysmal AF to sinus rhythm. These drugs are ineffective in patients with AFl.[1,2] Furthermore, class I antiarrhythmic agents exert negative inotropic and proarrhythmic effects probably related to their capacity to depress cardiac conduction. This has stimulated research to find antiarrhythmic drugs without negative inotropy and without a depressing effect on cardiac conduction, but with similar antiarrhythmic efficacy. From a theoretical point of view, antiarrhythmic drugs should increase refractoriness rather than depress cardiac conduction in order to terminate reentry arrhythmias.[3] Dofetilide (UK-68,798) is a new highly selective class III antiarrhythmic agent that has undergone extensive preclinical evaluation.[4-7] Dofetilide selectively prolongs refractoriness without any effects on conduction by blocking the potassium-outward channels.[6] In an open-label dose-ranging study, we investigated the efficacy and safety of intravenous dofetilide in patients with paroxysmal AF or AFl for the acute conversion to sinus rhythm.

Twenty-four consecutive patients (20 men and 4 women) aged 38 to 70 years old (mean 55 ± 10) were selected for this study which was approved by the institutional review board. All patients gave informed written consent before entering the study. Adult men and women (aged between 18 and 70 years) without childbearing potential were entered into the study if there was AF or AFl lasting <6 months with a ventricular rate >100 beats/min at rest. Exclusion criteria were severe congestive heart failure (New York Heart Association class III or IV), unstable angina pectoris or myocardial infarction, or both, of <6 weeks, concomitant therapy with antiarrhythmic drugs except treatment with digoxin, hypertension, a resting QTc interval >0.42, electrolyte imbalance (plasma potassium <3.5 mmol/liter, plasma magnesium <0.6 mmol/liter), Wolff-Parkinson-White syndrome, and other clinically significant diseases.

All patients were admitted to the coronary care unit and antiarrhythmic medication was discontinued for ≥ 5 half-lives. A complete medical history and physical examination, biochemical laboratory testing, chest x-ray and a 12-lead electrocardiography was performed before administration of the drug. If the chest x-ray showed signs of cardiac enlargement, additional 2-dimensional echocardiography was performed before start of treatment. The patients were observed for at least 1

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TABLE I Rate of Conversion to Sinus Rhythm with Intravenous Dofetilide

	AF	AFl
Dose		
Low-dose group	3/6*	1/2*
High-dose group/15 minutes	3/6	2/2
High-dose group/10 minutes	4/7	1/1
All treated patients	10/19	4/5
Duration of arrhythmia		
≤24 hours	4/6†	0/1†
>24 hours	6/13	4/4

*Difference not significant compared with high-dose groups.
†Difference not significant compared with >24 hours.
AF = atrial fibrillation; AFl = atrial flutter.

hour before administration of the drug to allow their condition to stabilize.

Three dose regimens were tested. The first 8 patients received 2.5 μg/kg as a constant infusion over a period of 15 minutes. If conversion from AF or AFl to sinus rhythm did not occur within 15 minutes after infusion, a second infusion of dofetilide (2.5 μg/kg) was administered (low-dose group). A second group of 8 patients received 4.0 μg/kg over 15 minutes and this was repeated if necessary (high-dose group/15 minutes). A third group of 8 patients received 4.0 μg/kg in 10 minutes, repeated if necessary after 15 minutes (high-dose group/10 minutes).

During and after each infusion period, electrocardiographic (leads V_2 or V_5) monitoring and vital signs were frequently obtained. Treatment was considered successful when sinus rhythm was reestablished ≤ 3 hours after start of the first infusion. An additional 12-lead electrocardiogram was recorded at the time of conversion to sinus rhythm and 24 hours after commencement of the initial infusion. The nonresponders were treated with other antiarrhythmic drugs or with direct-current cardioversion. Mean values ± standard deviations were given for continuous variables. The variables were analyzed by means of a paired t *test or Fisher's exact test where appropriate.*

Nineteen patients with AF and 5 patients with AFl entered this study. Recent onset (≤24 hours) AF was present in 6 (32%) patients and AFl in 1 (20%), whereas 13 (68%) had long-standing (>24 hours) AF and 4 (80%) had long-standing AFl. The mean duration of the arrhythmia before inclusion in the study was 32 ± 43 days (range 1 to 150). Mean anteroposterior left atrial size on 2-dimensional echocardiography was 39 ± 5 mm (range 31 to 53). Eighteen patients had no apparent cardiac disease, 4 had hypertensive heart disease and 2 had coronary artery disease.

Conversion to sinus rhythm was achieved in 10 (53%) of the 19 patients with AF and in 4 (80%) of the 5 patients with AFl. The rate of conversion to sinus rhythm with dofetilide compared with the received dose and duration of the arrhythmia is listed in Table I. The mean time required for conversion to sinus rhythm was 40 ± 52 minutes (range 3 to 100).

Blood pressure and electrocardiographic parameters were evaluated at baseline and during the first 24 hours after start of the study. Blood pressure remained unchanged. In patients without conversion to sinus rhythm the heart rate also remained unchanged. However, QTc intervals increased significantly from 419 ± 37 to 496 ± 37 ms ($p < 0.001$), but the QRS duration remained unchanged. In patients with AFl, a significant increase in flutter cycle length from 176 ± 22 to 232 ± 52 ms was noted ($p < 0.05$). In all treatment groups not a single adverse effect was observed.

Based on prior in vivo and vitro studies, dofetilide,[4–7] a new highly selective class III antiarrhythmic agent, was studied for rapid termination of paroxysmal AF and AFl in humans. In this dose-ranging study, intravenous dofetilide appears to be an effective and safe drug for converting paroxysmal AF and AFl to sinus rhythm. An interesting observation was the efficacy of dofetilide for terminating AFl, whereas class IC antiarrhythmic agents are usually ineffective for restoring sinus rhythm.[2] QTc intervals showed a significant increase after infusion of dofetilide, which is not surprising as the QTc interval largely represents the ventricular refractory period. No significant QRS widening was noted, indicating that the drug does not influence cardiac conduction. At all 3 doses, blood pressure remained unchanged and not a single adverse event was noted.

In this study, dofetilide showed an overall efficacy rate of 53% in patients with AF, whereas the overall conversion rate in patients with AFl was even 80%. Interestingly, 71% of all patients had long-standing AF or AFl. The results were too small to discriminate for dose-related efficacy. Several other class III antiarrhythmic agents have previously been studied for restoring AF and AFl to sinus rhythm, including amiodarone, sotalol and d-sotalol. After the administration of intravenous amiodarone, Benaim et al[8] showed a conversion rate of 90% in patients with AF, but they reported only a 50% conversion rate in patients with AFl. Sotalol seemed only moderately effective in converting patients with either paroxysmal AF or AFl to sinus rhythm.[9]

Both AF and AFl are generally considered to be based on reentry.[10] Compared with class I antiarrhythmic drugs, the blockade of cardiac potassium channels by dofetilide presents an alternative mechanism for terminating atrial arrhythmias by a selective prolongation of the refractory period without slowing of cardiac conduction, thereby terminating the reentrant circuit. The high efficacy of dofetilide in patients with AFl is remarkable. It is very likely that this finding can be attributed to its pure class III antiarrhythmic action. Nevertheless, dofetilide seems somewhat less effective in patients with AF. One questions why its efficacy is lower. Comparison of dofetilide with class I antiarrhythmic drugs may shed new light on the mechanisms of termination in reentrant arrhythmias.

In conclusion, dofetilide seems an effective and well-tolerated new antiarrhythmic agent for converting paroxysmal AF or AFl. However, no dose response relation was found in this limited number of observations. In particular, its successful outcome in usually drug-resistant AFl, frequently requiring direct-current cardioversion, is very promising and underscores the importance of selective class III antiarrhythmic action for terminating reentry tachycardias. Higher doses or a faster rate of administration, or both, should be tested to increase efficacy. A large-scale double-blind placebo-controlled study is necessary to confirm the initial efficacy of dofetilide for conversion of paroxysmal AF or AFl.

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Usefulness of Transesophageal Echocardiography for Diagnosis of Mitral Valve Prolapse

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Transthoracic 2-dimensional echocardiography (TTE) provides a very useful tool for assessing mitral valve anatomy and currently constitutes the procedure of choice in the diagnosis of mitral valve prolapse (MVP).[1,2] However, since the description by Levine et al[3] of the mitral annulus as a "saddle-shaped" structure rather than a planar structure, it has become apparent that the relation between the mitral valve and the mitral annulus cannot be completely evaluated from a single TTE view, and also, that this technique may occasionally induce MVP misdiagnosis in normal subjects.[4,5] Transesophageal echocardiography (TEE) allows an accurate recognition of mitral valve abnormalities and its use in the diagnosis of MVP has also been reported.[6] Recently, the introduction of biplane TEE has further enhanced our understanding of mitral valve anatomy, and consequently it seems attractive to speculate that the 3-dimensional information provided by this technique may help in the diagnosis of MVP. Accordingly, this prospective study was undertaken to define characteristic biplane TEE patterns in a consecutive series of patients with MVP.

Twenty consecutive patients with the diagnosis of MVP and adequate TTE studies, who were seen in our laboratory from January 1990 to August 1990, comprised the study group. Mean age was 44 ± 13 years and 14 patients (70%) were women. The diagnosis of MVP was performed according to classic clinical and echocardiographic findings.[2,7] On examination 13 patients (65%) had a midsystolic click and a late systolic murmur and TTE confirmed the clinical suspicions of MVP, whereas in the remaining 7 patients the diagnosis was based on TTE findings alone. After oral consent was obtained, patients entered a prospective protocol that included a TTE and subsequently a TEE study.

Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography.[8] An Aloka 870 machine with a 2.5 MHz transducer was always used. Echocardiographic recordings were stored on video tape with the possibility of frame-by-frame analysis, and subsequently, all studies were reviewed by 2 independent observers. M-mode recordings of the mitral valve were obtained at the level of the mitral valve tips from 2-dimensional images to avoid oblique cuts. M-mode criteria of MVP included (1) mid- to late systolic posterior motion (≥2 mm) of at least 1 mitral leaflet, and (2) holosystolic hammocking (≥3 mm) of any mitral valve leaflet.[8,9] Redundancy of mitral valve leaflets was assessed by measuring the thickness of the mitral valve in diastole at the midpoint of the EF slope. Mitral valve leaflets were considered to be thickened if ≥5 mm.[10] Other M-mode findings previously described as shaggy diastolic echoes, heavy cascading echoes, reduplication of systolic echoes and abutment of the mitral valve E point against the septum, were also analyzed. With TTE the movement of the mitral valve leaflets was studied from multiple conventional views. Special care was taken in visualizing the presence of billowing of the mitral valve leaflets into the left atrium and the exact location of the coaptation point of the mitral leaflets. Mitral valve annular size was measured in systole from the 4-chamber view and it was considered to be enlarged if >34 mm. The TTE diagnosis of MVP was established if a marked superior systolic displacement of the mitral leaflet was visualized with the coaptation point at or superior to the annular plane, and when mild or moderate superior systolic displacement of the mitral leaflets occurred in conjunction with either chordal rupture, mitral regurgitation on Doppler ultrasound, or annular dilatation.[7] A complete pulsed, continuous and color Doppler study was also obtained in

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every patient from the TTE approach to evaluate the presence and severity of mitral regurgitation. Severity of mitral regurgitation was graded I to III according to the size of the regurgitant jet area in relation to left atrial area in orthogonal views.[11]

TABLE I Echocardiographic Findings

		M-Mode		TTE			TEE			
Pt. No.	Age/Gender	LSPM	HH	SB	PCP	MR	SB	PCP	MR	RCh
1	20/F	–	+	+	+	II	+	+	II	–
2	23/F	+	–	+	+	–	–	+	–	–
3	23/F	+	+	+	–	II	+	+	II	+
4	27/M	–	–	+	+	–	+	+	I	–
5	35/F	+	–	+	+	–	+	+	–	–
6	37/M	+	–	–	+	II	+	+	II	–
7	38/F	–	+	–	+	–	+	+	I	–
8	39/F	–	–	+	–	II	+	+	III	+
9	39/M	+	+	+	+	–	–	+	–	–
10	45/M	+	–	+	+	–	+	+	II	–
11	50/F	+	+	+	–	II	+	+	III	+
12	51/M	–	–	+	+	–	+	+	II	–
13	52/F	–	–	+	+	–	+	+	–	–
14	52/F	+	–	–	–	II	+	+	II	–
15	58/F	–	–	+	+	I	+	+	II	–
16	58/F	+	+	–	+	–	+	+	–	–
17	58/M	+	–	+	–	I	+	+	II	–
18	59/F	+	–	+	+	II	+	+	II	–
19	60/F	+	–	+	+	–	+	+	I	–
20	60/F	+	–	+	+	–	+	+	II	–

HH = holosystolic hammocking; LSPM = late systolic posterior motion; MR = mitral regurgitation (graded I to III); PCP = protrusion of the coaptation point; RCh = ruptured chordae tendinae; SB = systolic billowing; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; – or + denotes absence or presence of the sign.

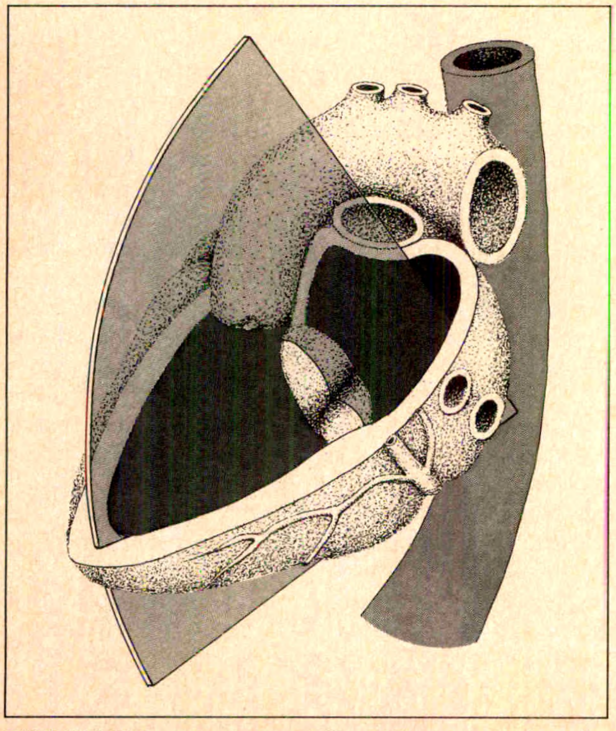

FIGURE 1. Schematic representation of the transesophageal longitudinal axis *(shadow)* showing both the anterior and posterior mitral valve leaflets in relation to the surrounding cardiac structures.

When TTE studies were completed all patients underwent a biplane TEE study (5 MHz transducer). Patients were studied in the fasting state after receiving sedation with 5 mg of intravenous diazepam and lidocaine spray in the oropharynx. With TEE, a 3-dimensional reconstruction of the relation between the mitral valve and the mitral annulus was attempted. With the longitudinal axis, a complete view of the posterior mitral leaflet was obtained (Figure 1). From the transverse plane the anterior mitral leaflet as well as the posteromedialis commissure were analyzed (Figure 2). With a more caudal position of the transducer this plane also permitted evaluating the posterior mitral leaflet. Again, with biplane TEE, care was taken to assess the presence and severity of leaflet billowing and to accurately determine the location of the coaptation point of the mitral valve. Pulsed and color Doppler studies of the mitral valve were subsequently performed to evaluate the presence and severity of mitral regurgitation, and this information was compared with the results of the TTE studies. With TEE color Doppler, the severity of mitral regurgitation (I to III) was assessed by planimetry of the area of the regurgitant jet as previously described.[12]

Continuous data are presented as mean ± standard deviation. The chi-square test, with the Yate's correction when indicated, was used to compare qualitative variables of TTE studies with those of TEE.

On M-mode studies, 10 patients (50%) had thickening of the mitral leaflets. A late systolic posterior motion of mitral leaflets was seen in 13 patients (65%) and a holosystolic hammocking of mitral valve leaflets was present in 6 patients (30%). Other signs of MVP included early diastolic anterior motion of the posterior mitral

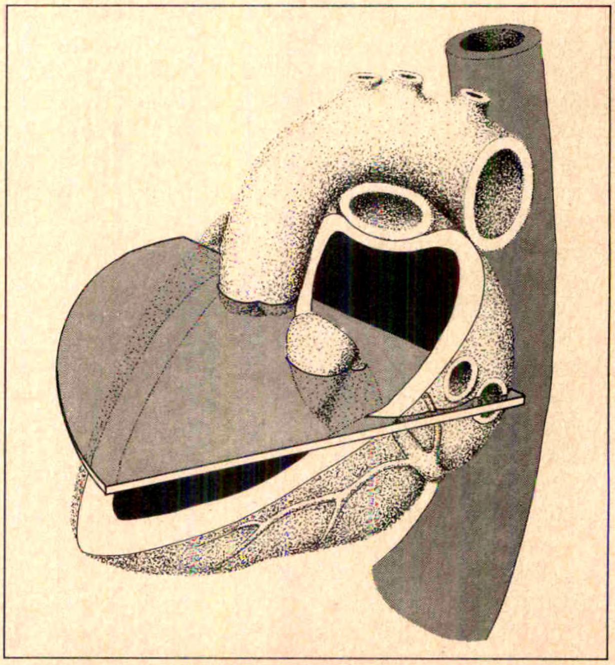

FIGURE 2. Schematic representation of the transesophageal transverse axis at the mitral valve level, showing the relation between the posteromedialis commissure and the anterior mitral leaflet.

valve leaflet (1 patient), shaggy diastolic echoes (2 patients), cascading diastolic echoes (1 patient), reduplication of mitral echoes (3 patients), and abutment of the mitral valve E point against the septum (2 patients). All patients showing any of these later echocardiographic signs also had at least 1 of the 2 major M-mode criteria for MVP. M-mode echocardiography was able to make the diagnosis of MVP in 15 of the 20 patients (75%) (Table I).

On TTE mitral valve annular size was 27 ± 8 mm, and 13 patients (65%) presented with mitral valve annular dilatation. Systolic billowing of mitral valve leaflets was recognized in 8 patients (40%) from the parasternal long-axis view and in 14 (70%) from the 4-chamber view. The coaptation point was beyond the mitral annulus from the parasternal long-axis view in 9 patients (45%) and from the 4-chamber view in 14 (70%). According to the previously considered TTE criteria of MVP, 9 patients had the first criteria, 5 had the second and 3 had both. With TTE color Doppler 9 patients had mitral regurgitation (Table I).

With biplane TEE, systolic billowing of either the anterior or posterior mitral valve leaflets into the left atrium was seen either in the longitudinal or in the transverse plane in 18 patients (90%) ($p < 0.001$ compared with parasternal long-axis TTE and p = not significant compared with both TTE views) (Figure 3). In 2 of these patients billowing was not appreciated from any TTE view. Biplane TEE demonstrated systolic displacement of the coaptation point beyond the mitral valve annulus in all 20 patients (100%) ($p < 0.05$ compared with TTE). In addition, this technique showed mitral valve chordae rupture in 3 patients (15%), which was not previously seen from the transthoracic approach. With color Doppler TEE, 15 patients (75%) had mitral regurgitation (Figure 4) (p = not significant compared with TTE studies). No complications were seen as the result of TEE.

The value of TTE in the diagnosis of MVP is well established.[9] However, the saddle-shaped morphology of the mitral annulus may induce the false appearance of superior displacement (into the left atrium) of the mitral leaflets, even in normal subjects, when only 1 TTE plane is used.[3] Preliminary data suggest the value of single-plane TEE in the diagnosis of MVP.[6,13] However, only biplane TEE provides the opportunity to image the mitral valve, from 2 different orthogonal planes, allowing a 3-dimensional understanding of the nonplanar structure of the mitral annulus. With the transverse plane it is possible to visualize the anterior mitral leaflet and usually the posteromedialis commissure (Figure 1). Alternatively, the longitudinal plane evaluates, in different cuts, both the anterior and posterior mitral valve leaflets. In particular we found this view of special value in the assessment of the movement of the posterior mitral leaflet (Figure 2). The information obtained from both planes allowed us to completely visualize the relationship between the mitral valve leaflet and its annulus. In our study with biplane TEE every patient showed an abnormally displaced mitral valve coaptation point within the left atrium and, in addition, 90% of them presented systolic billowing of the mitral valve leaflets. Therefore, biplane TEE was, in our experience, superior to conventional TTE in the diagnosis of MVP. Also for the diagnosis of mitral regurgitation, biplane TEE was more sensitive to TTE in the present series. This confirms our previous experience in a general patient population, suggesting that TEE is a more sensitive technique for detecting the presence of mitral regurgitation than TTE.[13]

Our study only analyzed a relatively small cohort of patients with classic clinical and echocardiographic criteria of MVP. All these patients had biplane TEE patterns indicative of MVP. However, although it would have been of major interest to determine whether TEE could be of complementary value to TTE to prevent MVP misdiagnosis, all patients in this series had MVP on bi-

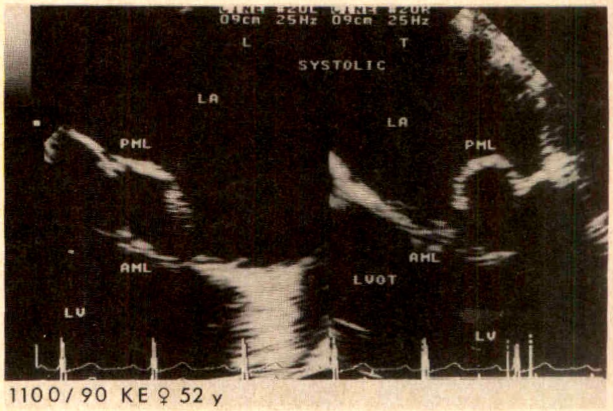

FIGURE 3. ***Left,*** **transesophageal echocardiogram from the longitudinal axis revealing billowing of the posterior mitral leaflet into the left atrium.** ***Right,*** **transverse plane showing relation between the anterior and posterior mitral leaflets and the posteromedialis commissure more clearly. There is marked billowing of the posterior mitral valve leaflet into the left atrium. AML = anterior mitral valve leaflet; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; PML = posterior mitral valve leaflet.**

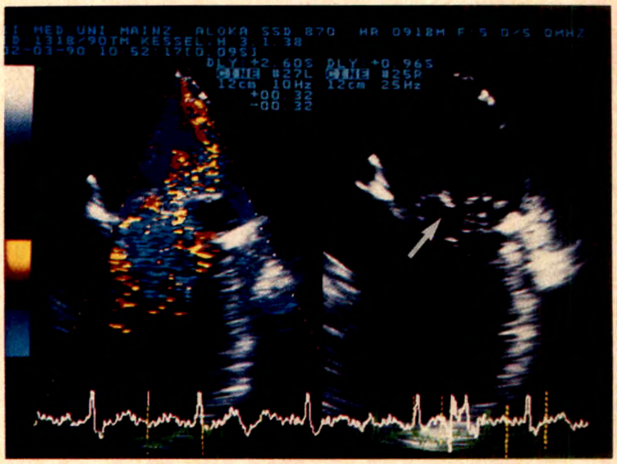

FIGURE 4. ***Left,*** **transesophageal echocardiogram from the longitudinal plane disclosing the presence of mitral regurgitation on color Doppler.** ***Right,*** **transverse plane from the same patient showing billowing of both mitral valve leaflets into the left atrium. The coaptation point of the mitral valve leaflets is also displaced into the left atrium** ***(arrow).***

plane TEE, so that the specificity of the technique could not be determined. In addition, we did not measure the degree of either displacement of the coaptation point into the left atrium or the severity of mitral valve billowing, and these factors could have diagnostic implications. Prospective studies including larger series of patients with the suspected clinical diagnosis of MVP will be required to determine absolute criteria for the diagnosis of MVP with biplane TEE and to define the specificity and sensitivity of this technique. Furthermore, the subset of patients in whom biplane TEE should be performed in order to obtain a more accurate diagnosis, and the value of this technique in the decision-making process involved in the management of patients with MVP needs to be defined.

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Efficiency of Disopyramide in Hypertrophic Cardiomyopathy During Stress States

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Disopyramide is thought to be efficient in treating most cases of hypertrophic cardiomyopathy.[1] Clinical symptoms, hemodynamic data at rest, and exercise duration are improved by disopyramide.[1-2] However, hemodynamic effects of a particular treatment can be different at rest and during exercise. Thus, propranolol has little effect on the intraventricular pressure gradient at rest, but may diminish the increment that occurs with exercise.[3] No data are available concerning the hemodynamic efficiency of disopyramide during exercise.

Cardiac echo-Doppler investigations were performed on patients with asymmetric hypertrophic cardiomyopathy (septum/posterior wall thickness >1.5). Subaortic flow velocity was first recorded at rest in the left lateral position. Outflow gradients were estimated from the peak velocities by Bernoulli's formula: pressure gradient = 4 (velocity^2). A submaximal dynamic exercise was then performed in the supine position on a cycloergometer. Subaortic flow velocity and heart rate were measured at peak exercise. Left ventricular obstruction was considered significant if subaortic flow velocity was higher than 3 m/s (36 mm Hg). Oral disopyramide was then prescribed at a dose of 6 to 8.5 mg/kg, according to clinical tolerance. A second cardiac echo-Doppler was performed 1 month after initiation of treatment. Plasmatic levels of disopyramide were measured during the echocardiographic study using an enzyme immunoassay (EMIT-ABBOTT®—therapeutic range 2 to 5 ng/ml). Student's paired t *test was used for statistical analysis.*

Nine patients were included in this open study (Table I). All patients had a significant obstruction: at rest in 7, and during exercise in 2 (nos. 7 and 8). All patients were in sinus rhythm. Eight patients were in New York Heart Association functional class I or II, and 1 was in class III (patient 9). Patient 3 did not perform exercise, because of dyspnea, tachycardia and rest obstruction. Tachycardia rapidly disappeared after hospital discharge, as shown by Holter recording. Thus, rest tachycardia could be related to anxiety. Patient 6 did not perform exercise, because of a very high rest obstruction (>150 mmHg). In all patients who performed the stress test, tolerance was good, without ventricular arrhythmias. After disopyramide administration, left ventricular pressure gradient significantly decreased at rest (p <0.05). In 4 patients (44%), a significant obstruction remained at rest. Left ventricular pressure gradient during exercise was significantly decreased after disopyramide (p <0.05). In all cases when exercise was performed, left ventricular pressure gradient and heart rate increased during exercise. Magnitude of increment of pressure gradient occurring with exercise was not significantly decreased after disopyramide (+40 mm Hg before vs +41 mm Hg after). At peak exercise, a significant obstruction was measured in 7 of 8 stress tests (87%). Only 1 patient (no. 7 with a latent obstruction at rest before treatment) had no significant obstruction at rest and during exercise. Disopyramide induced no significant changes on diastolic function (Table II).

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TABLE I Effect of Oral Disopyramide on Intraventricular Pressure Gradient and Heart Rate at Rest and During Exercise in Nine Patients Investigated by Stress Echo-Doppler

Patients			Before Disopyramide						Treatment		After Disopyramide					
			Rest		Exercise		Increment				Rest		Exercise		Increment	
No.	Age (yr) & Sex	Sept/PW	HR	Grdt	HR	Grdt	HR	Grdt	Drug Regimen (mg/day)	Plasm. Level (mg/L)	HR	Grdt	HR	Grdt	HR	Grdt
1	35M	24/14	85	68	114	103	+29	+35	500	0.9	86	40	133	90	+47	+50
2	15M	26/14	70	137	100	153	+30	+16	600	1.6	84	13	120	46	+36	+33
3	45F	23/10	138	127	*	*	*	*	500	1.9	130	100	*	*	*	*
4	44M	18/12	92	44	133	116	+41	+72	500	2	94	63	121	97	+27	+34
5	53F	21/14	67	111	131	151	+64	+40	500	2.1	60	71	126	119	+66	+48
6	40M	26/9	67	152	*	*	*	*	500	1.4	72	16	120	36	+48	+20
7	61F	27/13	70	30	90	54	+20	+24	400	2.4	75	5	100	13	+25	+8
8	23M	26/11	46	6	85	71	+39	+65	500	3.4	71	6	147	96	+76	+90
9	36M	24/10	105	73	134	98	+29	+25	500	1.6	79	25	150	73	+71	+48
Mean	39	25/12	82	83	113	107	+36	+40	500	1.9	83	38	127	69	+49	+41
SD	14	5/2	27	51	20	37	14	21	50	0.7	20	33	16	35	20	25

p <0.05

p <0.05

NS

*Not performed.

Grdt = gradient (mm Hg); HR = heart rate (beats/min); NS = not significant; Plasm. Level = plasmatic level; Sept/PW = septum/posterior wall thickness (mm).

TABLE II Effect of Oral Disopyramide on Diastolic Function in Nine Patients Investigated by Stress Echo-Doppler

Patients		Before Disopyramide						After Disopyramide					
No.	Age (yr) & Sex	HR	E	A	E/A	LVIRT	MVHT	HR	E	A	E/A	LVIRT	MVHT
1	35M	85	0.99	1.13	0.88	120	180	86	0.94	0.73	1.29	100	180
2	15M	70	1.53	0.58	2.64	80	180	84	0.23	0.50	0.46	80	170
3	45F	138	1.59	1.86	0.85	75	240	130	0.90	0.75	1.20	80	240
4	44M	92	0.77	0.56	1.37	100	220	94	0.92	0.71	1.29	100	190
5	53F	67	1.08	1.00	1.08	120	240	60	0.84	0.99	0.85	120	220
6	40M	67	0.62	0.91	0.68	140	250	72	0.52	0.83	0.63	120	230
7	61F	70	1.3	1.2	1.08	120	200	75	1.20	1.90	0.63	100	340
8	23M	46	1.6	0.28	5.7	100	200	71	1.04	0.80	1.30	120	140
9	36M	105	0.74	1.14	0.65	130	180	79	0.65	0.69	0.94	160	220
Mean	39	82	1.14	0.96	1.7	109	210	83	0.80	0.88	0.95	109	214
SD	14	27	0.38	0.46	1.6	22	28	20	0.29	0.40	0.33	25	57

A = late diastolic flow (m/sec); E = early diastolic flow (m/sec); HR = heart rate (beats/min); LVIRT = left ventricular isovolumetric relaxation time (ms); MVHT = mitral velocity half-time (ms).

In hypertrophic cardiomyopathy, the known efficiency at rest of oral disopyramide on left ventricular obstruction was partly confirmed in our patients during stress. Pressure gradients induced by exercise were significantly lower after disopyramide. Nevertheless, increments of heart rate and left ventricular gradient occurring during exercise were not significantly decreased after disopyramide administration. Furthermore, disopyramide did not prevent the occurrence of a significant obstruction in all stress tests except for 1. With propranolol, Flamm et al[3] did not find any significant increment during exercise. The anticholinergic activity of disopyramide and its inefficiency on β receptors could explain these results. Poor drug compliance or too small doses could be ruled out by our plasmatic level measurements.

Since the decrease of outflow obstruction is considered by some investigators as 1 of the major goals of medical treatment (because severity of symptoms appeared to be related to the intraventricular obstruction[4]), this efficiency should be permanent. Isolated tachycardia,[5] anxiety[4] or exercise[6] is known to increase the dynamic obstruction of hypertrophic cardiomyopathy. Thus, the efficiency of medical treatment of tachycardia due to anxiety (patient 3) or exercise appeared as a means to control obstruction in all circumstances, especially in those that are frequently associated with symptoms (e.g., exercise[5]). Adding small doses of β-adrenergic blockers could be a solution to this problem and should be evaluated.

The increase in exercise duration with oral disopyramide observed by Pollick[1-2] could be related to the hemodynamic effect on the left ventricular gradient in view of our results. This effect observed for Pollick's group of 9 patients was slight but significant ($p < 0.05$, paired *t* test). However, variable effects were observed; 2 of these patients who performed exercise had decreased exercise durations, and 1 had no change. A more uniform and coordinated pattern of relaxation due to the calcium antagonistic effect of disopyramide was previously advocated to explain this effect on exercise duration.[7] Our study does not support this hypothesis.

In conclusion, the efficiency of disopyramide appeared incomplete, because it decreased both rest and stress intraventricular pressure gradient, but did not prevent increase of the gradient occuring during exercise. Stress echo-Doppler appears to be a good noninvasive means to approach the mechanism of symptomatic improvement after initiation of treatment in hypertrophic cardiomyopathy and to repeatedly evaluate the permanent therapeutic effect of a drug.

Acknowledgment: We are grateful to Jean-Louis Lecroart, PhD, for assisting with statistical analysis.

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Assessment of Relative Sensitivities of Noninvasive Tests for Cardiac Amyloidosis in Documented Cardiac Amyloidosis

Michael Simons, MD, and Jeffrey M. Isner, MD

Noninvasive diagnosis of cardiac amyloidosis is a considerable diagnostic challenge. A variety of approaches including 2-dimensional echocardiography, computerized tomography, magnetic resonance imaging, electrocardiography and nuclear scintigraphy are used with varying degrees of effectiveness. The present study compares the relative sensitivity of these noninvasive tests in 15 patients with proven diagnosis of cardiac amyloidosis.

To be included in the study, patients had to satisfy 1 of the following 3 criteria: (1) tissue diagnosis of cardiac amyloidosis obtained by transvenous endomyocardial biopsy, (2) tissue evidence of cardiac amyloidosis obtained at necropsy, or (3) catheterization-documented hemodynamic evidence of restrictive cardiomyopathy in a patient with extracardiac tissue evidence of systemic amyloidosis. Fifteen such patients were identified through a retrospective review of medical records. Six were selected on the basis of endomyocardial biopsy, 8 because of necropsy findings, and 1 because of evidence of cardiac catheterization. Standard 12-lead electrocardiograms were reviewed in all patients. Voltage in limb and precordial leads was measured, and presence of pathological Q waves was noted. Measurements were obtained using the electrocardiogram closest to the time of diagnosis of cardiac amyloidosis or death. M-mode echocardiograms were used for measurements of ventricular wall thickness and cardiac chamber dimensions. The presence of sparkle on 2-dimensional echocardiograms was assessed in the parasternal short-axis view at the papillary muscle level. Left ventricular mass (muscle cross-sectional area or CSA) was calculated according to the following formula: $CSA\ (cm^2/m^2) = [\pi(LVEDD/2 + Th)^2 - \pi(LVEDD/2)^2]/BSA$, *where* $LVEDD$ = *left ventricular end-diastolic dimension,* Th = *left ventricular wall thickness, and* BSA = *body surface area. Results of technetium-99m pyrophosphate and diphosphonate scans were reviewed. The degree of myocardial uptake was graded on a 4-point scale: 0 = no uptake; 1+ = equivocal uptake; 2+ = definite uptake, but less intense than that of ribs; 3+ = intensity equal to that of ribs, but less than that of sternum; 4+ = intensity equal or greater than that of sternum.*

Clinical findings in the 15 patients are summarized in Table I, and the results of noninvasive studies are presented in Table II. Pathologic Q waves were the most frequently seen electrocardiographic abnormality and were present in 14 of 15 (93%) patients. Low voltage was present in 12 patients (80%). M-mode echocardiograms were available for review in all 15 patients. In addition, 11 patients had 2-dimensional echocardiograms. Left ventricular wall thickness was ≥12 mm in all patients (mean 15 ± 1.8 mm for the left ventricular free wall, and 15.1 ± 2 mm for the septum). Left ventricular end-diastolic diameter was normal (<5.5 cm) in all patients. Left ventricular systolic function was normal in all 11 patients with 2-dimensional echocardiograms available for review. Four patients had a "sparkling" appearance of the myocardium. The "sparkle" was most pronounced in the interventricular septum and less so in the ventricular free wall. There was no correlation between left ventricular wall thickness and presence of "sparkling" myocardium. Thirteen patients had pyrophosphate scans. Only 3 patients had a significantly (≥2+) positive myocardial uptake. There was no correlation between myocardial thickness (by ultrasound) and myocardial up-

TABLE I Clinical Findings in 15 Patients with Cardiac Amyloidosis

Pt.	Age (yr) & Sex	Amyloid Type	Diagnosis by	Associated Disease	Clinical Presentation	Pulmonary Congestion	Postural Hypotension
1	30 M	AA	Autopsy	JRA	SBO	+	+
2	73 M	AA	Biopsy	0	Neuropathy	+	+
3	69 M	AL/AA	Autopsy	0	NS	+	+
4	69 M	AL	Biopsy	0	NS	+	+
5	46 F	AL	Cath.	0	NS	+	+
6	63 F	AL	Autopsy	0	NS	+	+
7	79 M	AL	Autopsy	0	CRF	+	0
8	75 M	AL	Autopsy	MM	NS	+	0
9	48 M	AL	Autopsy	0	NS	+	+
10	64 F	AL	Biopsy	0	CHF	+	+
11	56 M	AL	Biopsy	0	NS	+	+
12	73 F	AL	Autopsy	0	NS	+	0
13	47 M	AL	Biopsy	0	Hematuria	+	+
14	67 M	AL	Biopsy	0	NS	+	+
15	47 M	AL	Autopsy	MM	NS	+	0

AA = secondary amyloidosis; AL = primary amyloidosis; Cath. = catheterization; CHF = congestive heart failure; CRF = chronic renal failure; JRA = juvenile rheumatoid arthritis; MM = multiple myeloma; NS = nephrotic syndrome; SBO = small bowel obstruction.

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TABLE II Results of Noninvasive Studies

Pt.	ECG/Low-Voltage	ECG Voltage $SV_1 + RV_5$	ECG Q Waves	ECG Conduction	ECG Arrhythmia	VS (mm)	LVFW (mm)	LVEDD (mm)	LA (mm)	LV Mass (cm^2/m^2)	Sparkle	TC Scan
1	+	13	No	Nl	0	17	16	46	30	17	+	0
2	0	18	V_1	Nl	0	19	19	37	32	14	0	0
3	+	7	3, aVF, V_{1-2}	Nl	SVT	16	14	47	36	13	0	1
4	+	5	2, 3, aVF	Nl	MAT	15	15	26	26	11	+	0
5	+	8	V_1	1°AVB	0	12	13	35	40	12	0	1
6	+	10	V_{1-3}	Nl	AF	17	17	40	32	18	0	2
7	0	27	V_1	LAH	AF	16	16	51	30	21	0	–
8	+	10	3, aVF, V_1	Nl	0	13	15	45	48	16	–	–
9	+	13	3, aVF, V_{1-3}	1°AVB	0	15	13	33	36	8	–	0*
10	+	7	V_{1-2}	1°AVB	0	16	16	35	35	13	0	3+
11	+	2	2, 3, aVF, V_{1-2}	LAH	AF	14	14	45	38	17	+	0
12	+	18	2, 3, aVF, V_{1-4}	LAH	AF	15	15	47	43	19	–	0*
13	0	17	3, AVF, V_{1-2}	Nl	0	12	12	32	38	20	+	0
14	+	11	V_{1-2}	Nl	SVT	15	15	45	50	9	–	0*
15	+	6	V_{1-4}	Nl	VT, SVT	22	21	42	46	22	+	2

AF = atrial fibrillation; 1°AVB = first-degree atrioventricular block; ECG = electrocardiographic; LA = left atrium; LAH = left anterior hemiblock; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVFW = left ventricular free wall; MAT = multifocal atrial tachycardia; Nl = normal; RV_5 = R wave in lead V_5; SV_1 = S wave in lead V_1; SVT = supraventricular tachycardia; TC = technetium scan; VS = ventricular septum; VT = ventricular tachycardia.
*Technetium–99m diphosphonate scan.

take of pyrophosphate. Similarly, there was no correlation between myocardial sparkle and pyrophosphate uptake. Voltage/mass analysis was performed for each study patient using the electrocardiogram recorded on the day of echocardiographic examination. Voltage was calculated as the sum of the S wave in lead V_1 *and the R wave in lead* V_5 *or* V_6 *(whichever was taller), and left ventricular mass was assessed by echocardiography. A diagram developed by Carrol et al*[1] *was used to plot the individual voltage/mass relations. In 12 patients (80%), the voltage/mass relation was in the range (muscle CSA* >10 cm^2/m^2 *BSA, voltage* <20 *mm) similar to that of symptomatic patients with cardiac amyloid in Carrol et al. The patient outside of this range because of a high voltage had history of severe hypertension. The other 2 patients outside of this range had low muscle cross-sectional areas.*

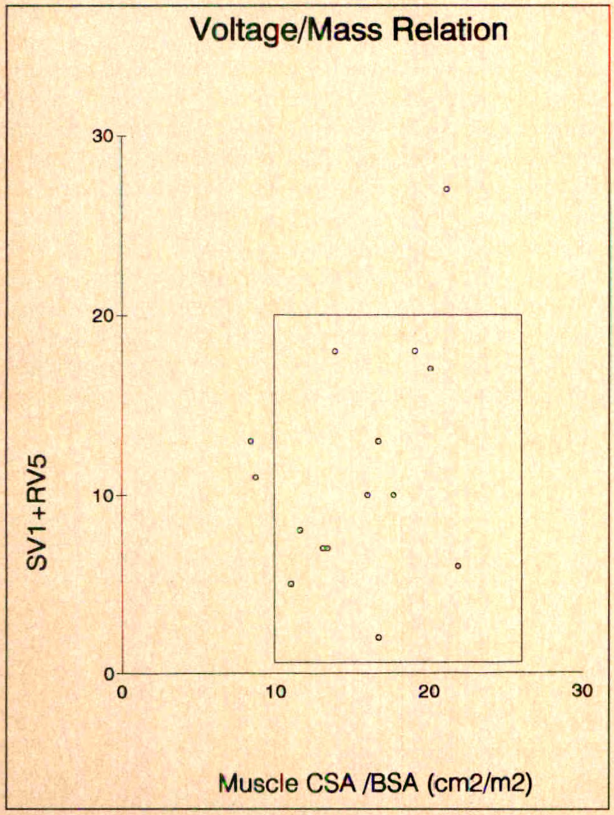

FIGURE 1. Electrocardiographic voltage is expressed as sum of height of S wave in lead V_1 (SV1) and of R wave in lead V_5 (RV5). Muscle mass is expressed as cross-sectional/body surface area (CSA/BSA) ratio. *Box* defines patients in symptomatic amyloid group according to criteria of Carrol et al.[1]

Diagnosis of cardiac amyloidosis frequently presents a challenge to clinicians despite the availability of a number of noninvasive techniques. A variety of electrocardiographic, echocardiographic and nuclear scintigraphic findings were described in these patients. However, there are few studies directly comparing different techniques in a well-defined group of patients. In this study we compared electrocardiographic, echocardiographic and scintigraphic findings in 15 patients with tissue or hemodynamic evidence of cardiac amyloidosis. Electrocardiographic documentation of low voltage[2] is often 1 of the first clues to the presence of cardiac amyloidosis and was seen in 80% of patients in the present study. This finding is nonspecific, occurring in a variety of conditions including pericardial and pleural effusions, emphysema, myxedema, obesity and coronary artery disease.[3] Echocardiography in patients with cardiac amyloidosis is frequently reported to show symmetric left ventricular wall thickening[4] and the sparkling appearance of the myocardium.[5] Both of these findings are nonspecific, with the latter described in Pompe's disease, hypoplastic left heart syndrome, hypertrophic cardiomyopathy and chronic renal failure, as well as in left ventricular hypertrophy of any cause.[6] Myocardial uptake of technetium-99m-labeled pyrophosphate was proposed as another marker of cardiac amyloidosis. However, results of the present study and similar results reported by Gertz et al[7] strongly suggest that technetium pyrophosphate scintigraphy has a very low sensitivity for cardiac amyloidosis. Our results suggest that none of the noninvasive parameters evaluated in this study for diagnosis of cardiac amyloidosis are highly sensitive. Thus, low voltage had a sensitivity of 80%, myocardial sparkling 45%, and technetium-99m–pyrophosphate uptake 23%. This low sensitivity, coupled with the previously mentioned low specificity, makes these findings unattractive for diagnosis of amyloidosis.

An alternative approach to noninvasive diagnosis of cardiac amyloidosis was suggested by Carrol et al[1] who noted that patients with cardiac amyloidosis tend to have low electrocardiographic voltages and high echocardiographic estimates of left ventricular mass. When the voltage/mass relation for cardiac amyloid patients is compared with that for patients with aortic valve (high voltage, high mass) or pericardial (low voltage, low mass) disease, clear differences emerge. Plotting voltage/mass relations for the patients in this study on a diagram developed by Carrol et al (Figure 1) would place 12 patients (80%) in a cardiac amyloid range (voltage <20 mm, mass >10 cm^2/m^2). This result makes the voltage/mass relation an attractive approach for diagnosis of cardiac amyloidosis. However, there are no reliable estimates of specificity for this technique.

In conclusion, the present study examined several frequently used findings obtained by noninvasive techniques with regard to their sensitivity for diagnosis of cardiac amyloidosis. Our results suggest that the sensitivity of both myocardial technetium uptake and echocardiographic observation of sparkling are low. However, voltage/mass relation diagrams appear to be a very promising technique for noninvasive diagnosis of these patients. The use and specificity of this technique need further study.

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Simultaneous Mechanical Clot Fragmentation and Pharmacologic Thrombolysis in Acute Massive Pulmonary Embolism

Mohammed Rafique Essop, MCRP, FCP, Shirley Middlemost, FCP, John Skoularigis, MD, and Pinhas Sareli, MD

Patients with acute massive pulmonary embolism have a high risk of death within a few hours after the major episode.[1] A number of studies have demonstrated accelerated clot lysis using urokinase[2,3] or streptokinase.[4–7] More recently tissue-type plasminogen activator has been shown to rapidly and, for the most part, safely lyse pulmonary emboli when given either by the peripheral intravenous[8,9] or intrapulmonary[9] route. Despite the established superiority of thrombolytic therapy over heparin anticoagulation for hemodynamically compromised patients with massive pulmonary embolism, there remains a group of patients in whom survival depends on more rapid relief of pulmonary vascular obstruction and right ventricular afterload. Surgical pulmonary embolectomy is associated with a prohibitive operative mortality and is usually regarded as a treatment of last resort. Because pulmonary vascular resistance increases with greater proximity of the thrombus to the main pulmonary artery, we reasoned that forceful ad-

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From the Division of Cardiology, Baragwanath Hospital, P.O. Bertsham 2013, and University of the Witwatersrand, Johannesburg, South Africa. Manuscript received June 11, 1991; revised manuscript received and accepted October 7, 1991.

TABLE I Clinical and Biochemical Features in Patients with Acute Massive Pulmonary Embolism

Pt. No.	Age (yr) & Sex	Interval* (hours)	Symptoms	Predisposing Factors	Systemic BP (mm Hg)	PO$_2$/PCO$_2$ (mm Hg)
1	31F	18	Dyspnea, chest pain	Postpartum	80/60	60/28
2	40M	36	Dyspnea, phlebitis	Iliofemoral thrombosis	90/60	52/40
3	47F	12	Syncope, chest pain	Calf vein thrombosis	60/	63/32
4	38F	6	Hemoptysis, chest pain	Pelvic mass	70/40	59/33
5	21F	21	Dyspnea	0	95/65	65/26

*Interval = from symptom onset to presentation. Blood gases measured on 40% oxygen.
BP = blood pressure; PO$_2$/PCO$_2$ = oxygen pressure/carbon dioxide pressure.

TABLE II Angiographic and Hemodynamic Findings Before and After Mechanical Clot Agitation and Bolus Intrapulmonary Streptokinase

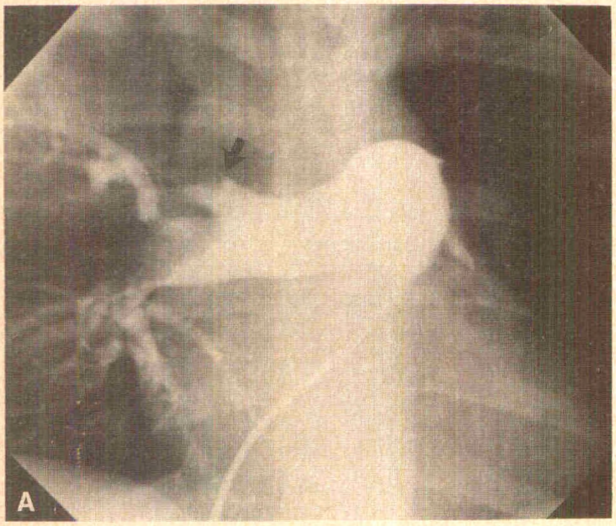
	Angiographic Score		BP		RVEDP (mm Hg)		PAP (mm Hg)		CI (liters/min/m^2)	
Pt. No.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	16	7	80/60	105/74	12	6	60/35	42/27	1.2	2.3
2	13	6	90/60	112/86	20	3	56/30	36/12	1.8	2.4
3	14	8	60/	90/60	28	8	64/35	36/16	1.7	2.8
4	15	6	70/40	100/55	18	9	85/40	34/16	1.8	2.5
5	12	4	95/65	118/84	21	5	52/38	36/18	2.1	3.1

Angiographic score, systemic blood pressure (BP), cardiac index (CI), pulmonary arterial pressure (PAP), and right ventricular end-diastolic pressure (RVEDP) for the 5 patients.

vancement of the clot more distally using a catheter introduced percutaneously into the pulmonary artery might attenuate the increase in pulmonary vascular resistance. A further advantage we reasoned would be enhanced clot exposure to lytic therapy by creation of multiple channels within the usually large emboli. The results of this approach in 5 patients with acute massive pulmonary embolism are presented in this report.

Over a 6-month period, 5 patients with acute massive pulmonary embolism with none of the usual contraindications to thrombolysis were admitted to Baragwanath Hospital, and form the basis of this report (Table I). Pulmonary embolism was defined as acute if symptom duration was < five days and massive if patients presented in a precarious clinical state with hypotension, hypoperfusion, cyanosis and right ventricular failure. The patient ages ranged from 21 to 47 years; there were 4 women and 1 man. Severe dyspnea was the presenting feature in 3 patients, pleuritic chest pain in 3, syncope in 1 and hemoptysis in 1 patient. A predisposing factor was present in all except 1 patient.

After initiation of a dobutamine infusion, right-sided cardiac catheterization was performed by the femoral approach. Right-sided hemodynamic data were obtained with either a Swan-Ganz or multipurpose catheter and cardiac output determined by the Fick method. Pulmonary angiography was performed using a National Institutes of Health, angled Pigtail or a Berman angiographic catheter positioned in the main pulmonary artery. Mainstream pulmonary angiography was performed on cut film or cineangiography using sodium meglumine ioxaglate (Hexabrix). Mechanical clot agitation was performed using a multipurpose end-hole catheter and an 035 guidewire. After positioning the catheter in the region of interest, an attempt was made to cross the occluding thrombus with the guidewire. In



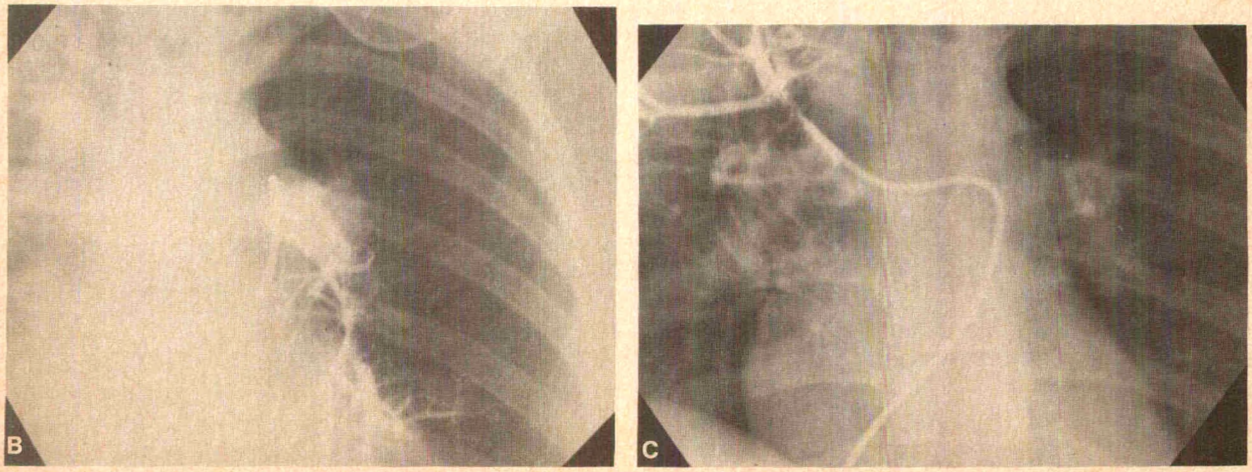


FIGURE 1. *A*, baseline pulmonary angiogram from patient 1 showing absent perfusion on the left and cutoff of right upper lobe pulmonary artery segment *(arrow)*; *B and C*, restoration of left lower *(B)* and right upper *(C)* lobe perfusions after advancement of multipurpose catheter.

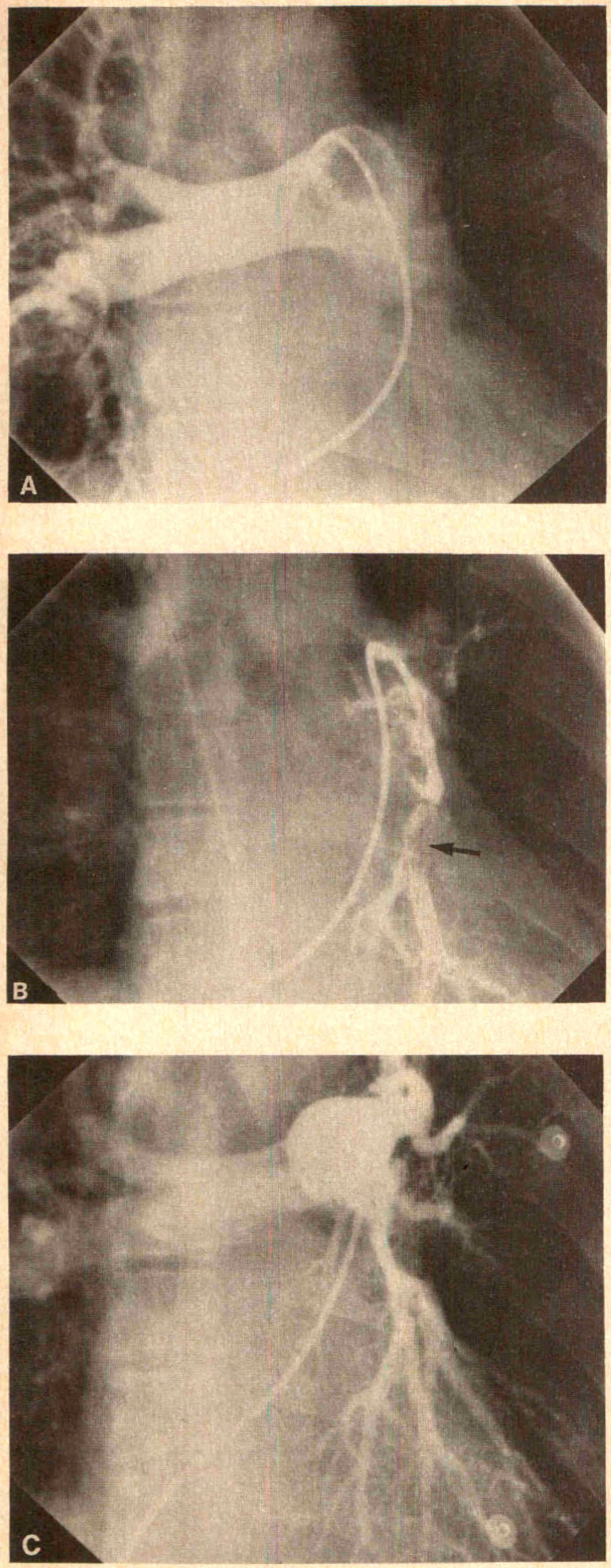


FIGURE 2. ***A,*** **baseline mainstream pulmonary angiogram from patient 4 showing absence of perfusion in left lung.** ***B,*** **after forceful catheter advancement, flow to the left lower zone is restored. Filling defects indicating intraluminal thrombus are visible** ***(arrow).*** ***C,*** **repeat angiography 1 hour after intrapulmonary streptokinase. Filling defects have disappeared and some flow has been restored to left upper and midzones.**

cases where this was unsuccessful the catheter with the guidewire positioned at its tip was advanced in the anticipated direction of the pulmonary artery with frequent hand injections of contrast to delineate distal anatomy. Thrombolytic therapy was then begun by infusing 600,000 U of streptokinase over 30 minutes into the main pulmonary artery. Right-sided cardiac hemodynamic assessments and pulmonary angiography were repeated and the patient transferred to an intensive care unit with a Swan-Ganz catheter in position where Streptokinase infusion at 100,000 U/hour was continued for a further 12 hours. Objective analysis of pulmonary angiograms was performed according to the criteria set by investigators of the Urokinase Pulmonary Embolus Trial.[2]

Angiographic and hemodynamic variables are detailed in Table II. Pretreatment angiographic scores ranged from 12 to 16. The worst possible score is 18, suggesting that all 5 patients had significant angiographic abnormality. After mechanical clot fragmentation and bolus streptokinase there was a significant decrease in angiographic score, from 14 ± 1.6 to 6.2 ± 1.5 (Figures 1 and 2), with a concomitant increase in systemic blood pressure and a decrease in right ventricular end-diastolic and pulmonary artery pressures (Figure 3).

One patient died 2 weeks after hospital discharge. One episode of major bleeding (groin hematoma) and 2 of minor bleeding were noted.

This study demonstrates the efficacy of combined clot advancement and fragmentation and thrombolytic therapy in patients with acute massive pulmonary embolism. The lack of similarity between our patients and those enrolled in other thrombolytic trials is obvious. In the study by Goldhaber et al,[8] patients in shock were excluded. Although patients in the trial reported by Verstrate et al[9] were more compromised, only 7 of 34 had a systemic blood pressure <100 mmHg and the mean pulmonary artery pressure before thrombolytic infusion was only 31 mm Hg. In contrast, all patients in this study were in a state of imminent cardiovascular collapse with systemic hypotension, hypoxemia and significant pulmonary arterial hypertension in whom a high mortality would have been expected. Mortality in a similar group of patients subjected to surgical embolectomy would be in the order of 30%.[10] Despite the severity of illness in our patients there were no in-hospital deaths and only 1 death 2 weeks

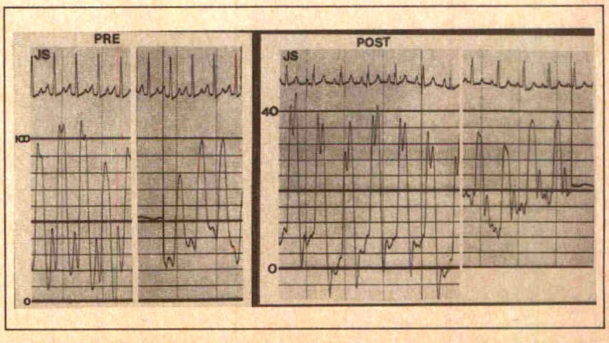


FIGURE 3. Right ventricular and pulmonary arterial pressures in patient 4 before (PRE) and after (POST) therapy showing significant reduction in pressures.

after hospital discharge presumably due to a recurrent pulmonary embolus. Additionally, there was a rapid amelioration of the hemodynamic state with an increase in systemic blood pressure and blood oxygenation and a decrease in pulmonary artery pressures. Further advantages of the technique that we have described are the ability to institute it rapidly and its ability to be performed by most interventional cardiologists.

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Patency of Ductus Arteriosus in Pulmonary Atresia and Ventricular Septal Defect

Hofbeck et al[1] reported on the survival of children with pulmonary atresia and ventricular septal defect, and in their Table I that the median age at the first palliative operation for patients with confluent pulmonary arteries supplied by a unilateral ductus arteriosus was 3 days. These data are in contrast with our experience. In a study of natural history of ductus arteriosus in infants with pulmonary atresia we found that patients with associated ventricular septal defect, confluent pulmonary artery and a single ductus arteriosus (32 cases) presented a delayed closure of ductus arteriosus compared with that of those with intact ventricular septum (58 cases).[2] All patients underwent angiocardiography, and the diagnosis was confirmed at surgery. Most children (52 of 58, 89.7%) with pulmonary atresia and intact ventricular septum needed surgery in the first week of life ($p < 0.0001$), whereas in the group with ventricular septal defect 16 of 32 (50%) patients underwent surgery after the first month ($p < 0.0001$) and 8 (25%) after the third month of life. In our patients with pulmonary atresia, ventricular septal defect, confluent pulmonary artery and single ductus arteriosus, mean age at surgery was 206 days (standard deviation 72.5).

The morphology of ductus arteriosus[3,4] may explain its persistent patency in cases with pulmonary atresia and ventricular septal defect tetralogy of Fallot type. This phenomenon may have important clinical implications regarding the timing and choice of surgical procedures, because not all these patients need surgery in the first week of life.

Bruno Marino, MD
Rome, Italy
12 August 1991

Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

1. Hofbeck M, Sunnegardh JT, Burrows PE, Moes CAF, Lightfoot N, Williams WG, Trusler GA, Freedom RM. Analysis of survival in patients with pulmonic valve atresia and ventricular septal defect. *Am J Cardiol* 1991;67:737–743.
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The Bedside Valsalva Maneuver in the Diagnosis of Congestive Heart Failure

It was with chagrin that I read the recent paper by Ghali et al[1] dealing with the bedside diagnosis of heart failure and found no mention of the Valsalva maneuver in their clinical protocol. This maneuver, described nearly 300 years ago,[2] is used at the bedside by many cardiologists today solely as a provocative test for the evaluation and differential diagnostic assessment of patients with a systolic cardiac murmur. However, of greater potential importance and wider use is its performance by the patient during careful auscultatory determination of the brachial systolic arterial pressure response using routine sphygmomanometric apparatus.[3] Correlation between impaired left ventricular systolic function, chest radiographic evidence of pulmonary venous hypertension, and the noninvasively determined sphygmomanometrically monitored arterial blood pressure response during Valsalva maneuver has been extensively documented in both the acute[4] and chronically ill patient.[5-8] Furthermore, the arterial pressure response during the bedside Valsalva maneuver has greater predictive value for abnormally elevated left ventricular end-diastolic pressure than any other conventionally sought physical diagnostic sign.[5] However, the response in patients with isolated left ventricular diastolic dysfunction has not been specifically studied, and determination of its predictive value in the patient population reported by Ghali et al would have been interesting.

Michael J. Zema, MD
Patchogue, New York
13 August 1991

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Correction

Anticardiolipin Antibody Titers in Patients with Myocardial Infarction (September 15, 1991: pages 830–831). On page 831, the names of the co-authors of this letter were mistakenly omitted. The authors of this letter are: D. Foley-Nolan, MB, MRCPI; Robert Woods, BSc, PhD; Lubna Choudhry, MB, MRCPI; Peter Byrne, MB, BCh; Declan Sugrue, MD; Robert J. Coughlan, MD; and Ciaran Barry, MD.

FROM THE EDITOR

Doctors, Save Your Money Because There Will Be Less in the Future

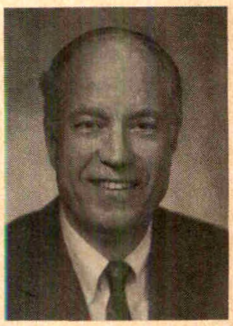
The November 1991 issue of *The Annals of Thoracic Surgery* published the first Ralph D. Alley lectureship which was given by Dr. Harry Schwartz and entitled "The future of American thoracic surgery."[1] Dr. Schwartz, trained as an economist, is a writer whose pieces have appeared in such publications as the *Wall Street Journal*, *New York Times*, and *USA Today* and most commonly in *The American Medical News*. His address was so "right on the mark" that I believe his comments deserve a wider audience, and that they are applicable to all branches of medicine and to all our citizenry. His major points:

1. *American medicine today is more effective than ever in history, is doing more good things for more Americans than ever in history, and is responsible both for many of the good things in the United States and many of the problems.*

Example: Despite acquired immunodeficiency syndrome (AIDS) and the relative higher mortality in the black population, total *infant mortality* has declined steadily each year in the USA for at least 30 years so that every year it is the lowest in history. In 1991, the infant mortality in the USA was about 9.5 deaths/1,000 live births, which means that less than 1 baby in 100 in the USA will die early. Several decades ago the infant mortality was 90 deaths/1,000 live births. Thus, the infant mortality has decreased 90% in my lifetime and in the lifetime of Dr. Schwartz. In contrast, in Russia the infant mortality rate is about 25 deaths/1,000 births, 2.5 times the rate in the USA. That more babies now survive in the USA creates the problem of more babies and eventually more adults to take care of.

Example: Life expectancy, i.e., the average length of life of people who die this year, continues to increase except for that of the black male which is declining, mainly because of homicides. The proliferation of the elderly — a success of medicine — in turn creates enormous problems and costs.

2. *Physicians as a group are not liked by the American public because doctors are regarded as too rich and they got rich by profiteering on human misery.* Although most individuals like their own physicians, doctors as a group are liked by few individuals. The median income of physicians in the USA is about $130,000 and most Americans consider that too much. Over 20% of cardiovascular surgeons earned over $600,000 in 1989 and their median income was $300,000. Again, figures considered "too much" by most Americans. Moreover, there is a widespread impression that much of what physicians do, and particularly what surgeons do, is unnecessary. Thus, the public (including politicians), which means the payers, is going to do everything possible to compress the earnings of physicians (also those of the hospitals, the pharmaceutical makers, etc.).



3. *Health-care costs are exploding because most Americans get "free" or "almost free" care and the demand for it is unrestrained.* Although about 15% of the US population (roughly 37 million persons) has no health insurance, about 85% of the population (roughly 212 million persons) has health insurance and it is pretty good health insurance. Because the potential demand for free medical care is *infinite*, those 212 million, whose care is not coming directly from their pocket, want the very best care available and they want it when they want it. The problem, of course, is that human resources are limited, i.e., *finite*, but the demand for them is out of control. In 1991, health care in the USA cost nearly $700 billion, which means about $2,800 for every person in the USA. And the US government is bankrupt. The national debt is now in excess of $3 trillion (A trillion dollars has 12 zeros in it, a million dollars, 6 zeros.). In 1991 alone, the US government increased its debt by $400 billion, which means 400,000 million dollars! Thus, the deficit for 1991 alone was 57% of the health care costs in 1991. And the only reason the USA can finance such a huge shortfall each year is because foreigners have been willing to buy our debt and buy it, amazingly enough, in US dollars whose value continues to decrease. The consequence of this debt will be that fees paid to and incomes earned by physicians will be more and more set by third-party payers. In 1992, the government will no longer pay fees for "routine electrocardiogram readings" which are being folded into the office visit. The following year, it may be the echocardiogram. The pressure on the US government is now so enormous that it will continue to cut what it pays for medical care.

4. *What physicians can do.* Probably very little but Schwartz recommends *better communication with patients*. It worked for the British Medical Association when the British government tried to revolutionize the British National Health Service and turn it, in effect, into one great big HMO. The British doctors communicated with British patients who made the Thatcher reform so unpopular that she lost her job. The handwriting is getting clearer — physicians in the foreseeable future will not be allowed to do everything to their patients that they are scientifically able to do. We must all communicate better.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

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[1] Schwartz H. The future of American Thoracic Surgery. *Ann Thorac Surg* 1991;52:1039–1043.

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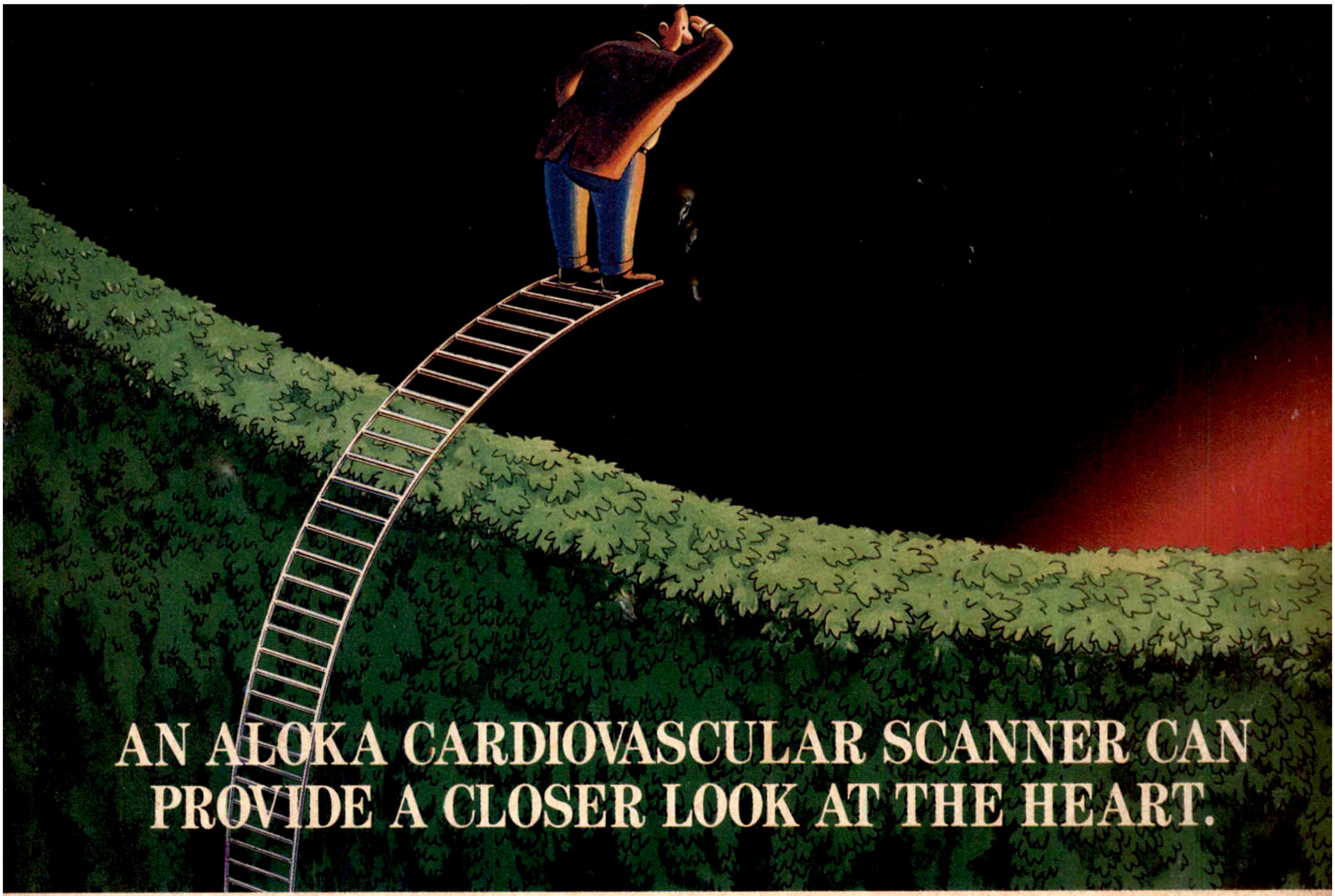
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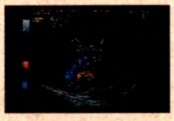

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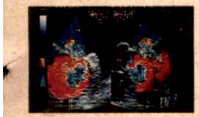

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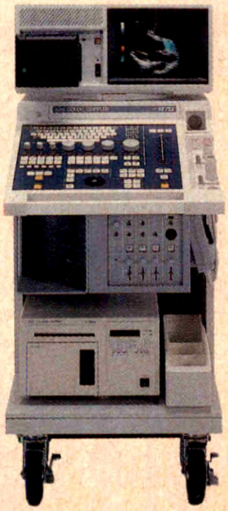

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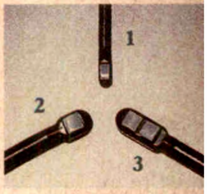

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PREVENTIVE CARDIOLOGY

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Role of Water-Soluble Dietary Fiber in the Management of Elevated Plasma Cholesterol in Healthy Subjects

William L. Haskell, Gene A. Spiller, Christopher D. Jensen, Brenda K. Ellis, and Joan E. Gates

Guidelines for the use of various water-soluble dietary fibers (WSDF) in the management of elevated plasma cholesterol are not well-established. Consequently, 4 randomized, placebo-controlled studies were conducted with healthy men and women (plasma cholesterol >5.17 mmol/liter; >200 mg/dl) to explore the plasma lipid-lowering effects of WSDF. Despite the WSDF classification of acacia gum, when it is consumed for 4 weeks as the sole WSDF source (15 g of WSDF/day) or primary source in a WSDF mixture (17.2 g of WSDF/day: 56% derived from acacia gum), it did not produce a significant lipid-lowering effect. When 15 g of WSDF/day consisting of psyllium husk, pectin, and guar and locust bean gums was consumed for 4 weeks, lipid-lowering effects resulted (total cholesterol 8.3%, low-density lipoprotein cholesterol 12.4%; $p < 0.001$) that were comparable to changes achieved with 10 g of WSDF/day from high-viscosity guar gum. A diet rich in selected WSDF may be a useful adjunct to the dietary management of elevated plasma cholesterol.

440

Role of Diet and Exercise in the Management of Hyperinsulinemia and Associated Atherosclerotic Risk Factors

R. James Barnard, Erika J. Ugianskis, Deborah A. Martin, and Stephen B. Inkeles

Hyperinsulinemia, hypertension, hypertriglyceridemia and obesity are all independent risk factors for coronary artery disease. The clustering of these risk factors in the same patient has been termed "the deadly quartet." This study was conducted to investigate the effects of an intensive, 3-week exercise and diet intervention on these risk factors in 13 diabetic patients, 29 insulin-resistant patients and 30 persons with normal insulin. Significant reductions were found in all risk factors for the group as a whole. For the subgroups only small reductions were found in those with normal insulin levels, whereas major reductions were found in the other 2 groups, especially diabetic patients. Although there was some weight loss in all 3 groups, most patients in the diabetic- and insulin-resistant groups did not achieve a normal weight despite normalization of many of the

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other risk factors. Initially, 15 patients had all of the characteristics of the deadly quartet, but at the end of the program only 3 still had all of the characteristics.

CORONARY ARTERY DISEASE

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ST-Segment Depression During Dipyridamole Infusion, and Its Clinical, Scintigraphic and Hemodynamic Correlates

Flordeliza S. Villanueva, William H. Smith, Denny D. Watson, and George A. Beller

The clinical, hemodynamic and scintigraphic correlates of ST-segment depression during intravenous dipyridamole infusion were studied in 204 consecutive patients undergoing dipyridamole stress thallium-201 (Tl-201) imaging for evaluation of coronary artery disease. Of 182 patients with a diagnostic baseline electrocardiogram, 15% developed ST depression after intravenous dipyridamole. By univariate analysis, patients with ST depression, compared with those without, were older and more likely to experience chest pain, and had a higher rate-pressure product after dipyridamole. These patients were also more likely to exhibit Tl-201 redistribution and had a greater number of redistribution defects. By multivariate analysis, the strongest correlate of ST depression was the number of segments demonstrating Tl-201 redistribution. Other independent multivariate correlates were occurrence of chest pain, heart rate after dipyridamole, and age. Thus, the determinants of dipyridamole-induced ST depression include the extent of myocardial hypoperfusion, as well as indexes of myocardial oxygen demand.

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Effect of Dipyridamole Therapy on Myocardial Ischemia in Patients with Stable Angina Pectoris Receiving Concurrent Anti-ischemic Therapy

Marilyn McFarland Barbour, Carol Ewing Garber, Kailash C. Agarwal, Rahul Malhotra, and Gary V. Heller

The effects of oral dipyridamole (75 mg 3 times daily) on graded exercise test performance and anginal symptoms were evaluated in 15 men with coronary artery disease using a randomized, double-blind, placebo-controlled, crossover design. Patients were maintained on previously prescribed cardiac medications throughout the 6-week study. There was no significant difference between dipyridamole and placebo treatments with regard to the time to onset of 0.1 mV ST-segment depression, angina or peak exercise. Anginal diaries and ambulatory electrocardiographic monitoring revealed no alteration in frequency of episodes during treatment with dipyridamole and placebo. It is concluded that chronic oral dipyridamole therapy given in a dosage currently used for its antiplatelet effects does not adversely affect exercise performance, daily anginal episodes or ambulatory ischemia in patients receiving concurrent anti-ischemic medication.

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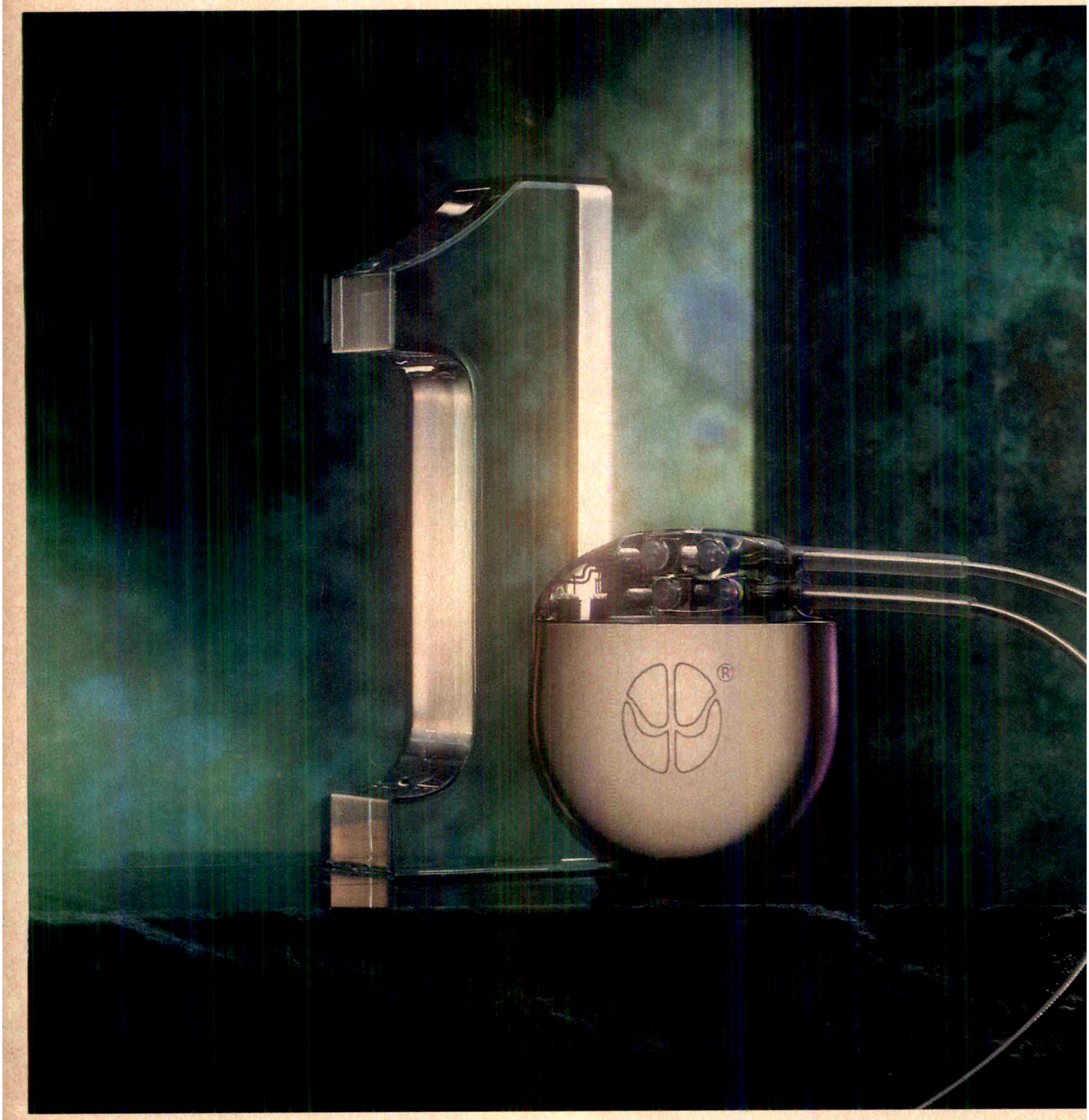

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**Barbieri D, Percoco G, Toselli T et al. AV delay and exercise stress test: Behavior in normal subjects. PACE 1990; 13:1724-1727. See also Technical Manuals for all products listed.

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Plasma Platelet-Derived Growth Factor Levels in Coronary Circulation in Unstable Angina Pectoris

Hisao Ogawa, Hirofumi Yasue, Ikuo Misumi, Takenobu Masuda, Ken Okumura, Satoko Bannai, Naoki Takanashi, and Yutaka Tsukada

To examine whether plasma platelet-derived growth factor (PDGF) levels are elevated in the coronary circulation of patients with unstable angina, the plasma PDGF levels in the coronary sinus and aortic root were simultaneously examined in 14 patients with unstable angina, 15 with stable exertional angina, and 15 control subjects. The mean plasma PDGF level in the coronary sinus was significantly higher in patients with unstable angina than in those with stable exertional angina and in control subjects. However, there were no significant differences in mean plasma PDGF levels in the aortic root among the 3 groups. It is concluded that PDGF release is increased in coronary circulation in unstable angina.

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Platelet Function After In Vivo and In Vitro Treatment with Thrombolytic Agents

Giampiera Bertolino, Patrizia Noris, Mario Previtali, Gabriella Gamba, Maurizio Ferrario, Nadia Montani, and Carlo L. Balduini

Ex vivo platelet function was studied in 24 patients with acute myocardial infarction treated with streptokinase or recombinant tissue-type plasminogen activator. At the end of drug infusion, platelet aggregation was significantly reduced with respect to 10 patients not receiving thrombolytic treatment. Three days later, platelet aggregation of subjects receiving streptokinase or recombinant tissue-type plasminogen activator was not significantly different from that of untreated patients. The functional defect of platelets observed after thrombolytic drugs was obtained by in vitro incubation of platelet-rich plasma with streptokinase.

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Identification of Patients at High Risk for Recurrence of Sustained Ventricular Tachycardia After Healing of Acute Myocardial Infarction

Luz Maria Rodriguez, Rudolfo Oyarzun, Joep Smeets, Johannes Brachmann, Claus Schmitt, Pedro Brugada, Peter Geelen, György Lipcsei, Adelin Albert, and Hein J. J. Wellens

A prognostic index for nonfatal recurrences of ventricular tachycardia (VT) was developed using a retrospective analysis of 206 patients with sustained monomorphic VT or ventricular fibrillation (VF) after healing of acute myocardial infarction. Three clinical variables were found to be of value using stepwise logistic discriminant analysis of the study group: interval of myocardial infarction to arrhythmia (<2 months = 1; 2 to 6 months = 2; >6 months = 3), drug therapy with or without sotalol (with = 1; without = 2), and VT or VF as the presenting arrhythmia (VT = 1; VF = 2). The prognostic index was: $3.41 - (0.56 \times \text{interval}) - (1.94 \times \text{therapy}) + (0.86 \times \text{arrhythmia})$. When prospectively evaluated in a test group of 158 patients with sustained monomorphic VT or VF after healing of acute myocardial infarction, 2 risk classes of patients were

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identified: a high-risk group (61% VT recurrences) corresponding to those with a negative index, and a low-risk group (4% VT recurrences) consisting of those with a positive index. This prognostic index may be used in selecting treatment of patients with VT or VF after healing of acute myocardial infarction.

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Correlation of the Complete Version of the Selvester QRS Scoring System with Quantitative Anatomic Findings for Multiple Left Ventricular Myocardial Infarcts

Dorina C. Sevilla, Nancy B. Wagner, Robert Pegues, Steven L. Peck, Eileen M. Mikat, Raymond E. Ideker, Grover Hutchins, Keith A. Reimer, Donald B. Hackel, Ronald H. Selvester, and Galen S. Wagner

This study of 32 patients with anatomically documented multiple infarcts describes the correlation between myocardial infarct size estimated by the complete version of the Selvester QRS scoring system and that documented by pathoanatomic studies. There was a significant correlation ($r = 0.44$; $p = 0.01$), but this was lower than that previously reported for single infarcts.

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Percutaneous Transluminal Coronary Rotary Ablation with Rotablator (European Experience)

Michel E. Bertrand, Jean M. Lablanche, Fabrice Leroy, Christophe Bauters, Peter De Jaegere, Patrick W. Serruys, Jurgen Meyer, Ulrich Dietz, and Raimund Erbel

Rotary ablation with Rotablator™ was performed in 129 patients. The overall primary success was 86%. Myocardial infarction (Q-wave and non-Q-wave) occurred in 10 patients. Urgent bypass grafting was undertaken in 2. No deaths related to the procedure occurred. Follow-up angiography was performed in 74 patients (60%) and the overall angiographic restenosis rate was 37.8%.

475

Quantitative Angiographic Follow-Up of the Coronary Wallstent in Native Vessels and Bypass Grafts (European Experience—March 1986 to March 1990)

Bradley H. Strauss, Patrick W. Serruys, Michel E. Bertrand, Jacques Puel, Bernhard Meier, Jean-Jacques Goy, Lukas Kappenberger, Anthony F. Rickards, and Ulrich Sigwart, with the technical assistance of Marie-Angèle Morel and Eline Montauban van Swijndregt

From March 1986 to March 1990, 265 patients (308 lesions) were implanted with the coronary Wallstent. Quantitative angiographic follow-up was performed in 82% of patients. The overall occlusion rate was 15%. Restenosis according to 2 criteria (loss in minimal luminal diameter >0.72 mm, diameter stenosis >50% at follow-up) was 43 and 27%, respectively. Native vessels had a higher in-hospital occlusion rate than bypass vessels (19 versus 8%), although the late restenosis rate was significantly greater in the latter (minimal luminal diameter 54 vs 34%, $p = 0.016$; diameter stenosis: 39 vs 18%, $p = 0.005$). One-year mortality was 6% in native vessel patients and 8% in bypass graft patients. Actuarial event-free survival (death, myocardial infarction, bypass surgery or angioplasty) was

46% at 40 months in the former group and 37% at 20 months in the latter. In-hospital occlusions remain a major problem with this device, particularly in native vessels. Restenosis continues to limit the early benefits of stenting, particularly in bypass grafts.

482

Effects of the Dipyridamole Test on Left Ventricular Function in Coronary Artery Disease

Herman O. Klein, Reuven Ninio, Shlomo Eliyahu, Avinoam Bakst, Alex Levi, Hadassah Dean, Victor Oren, Bruno Beker, Elieser Kaplinsky, Shlomo Gilboa, and Elio Di Segni

To determine the hemodynamic effect of the dipyridamole stress test, radionuclide ventriculography was performed before and after intravenous injection of dipyridamole in 113 patients with coronary artery disease and in 32 normal subjects. Ejection fraction responded abnormally in 98 patients (87%), decreasing from 49 ± 11% to 43 ± 13% ($p < 0.0001$), whereas it increased in 29 normal subjects (90%). Wall motion worsened distinctly in 75 patients (66%), and pressure/volume ratio deteriorated in 72%. Thus, dipyridamole generally affects left ventricular function in a way that indicates that it induces true myocardial ischemia and not just inhomogeneous increases in blood flow in patients with coronary artery disease.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

489

Improvement in Left Ventricular Systolic Function After Successful Radiofrequency His Bundle Ablation for Drug Refractory, Chronic Atrial Fibrillation and Recurrent Atrial Flutter

Gottfried Heinz, Peter Siostrzonek, Gerhard Kreiner, and Heinz Gössinger

The impact of rapid atrial fibrillation and its control by radiofrequency His bundle ablation on left ventricular (LV) function was studied. The data obtained indicate that rapid atrial fibrillation may significantly impair LV systolic function and that this depression in myocardial mechanics is reversible on successful control of rapid ventricular response. The observed improvement of fractional shortening was mainly due to a significant decrease in LV end-systolic dimension.

493

Frequency of Recurrent Atrial Fibrillation After Catheter Ablation of Overt Accessory Pathways

Michel Haissaguerre, Bruno Fischer, Thierry Labbé, Philippe Lemétayer, Paul Montserrat, Christophe d'Ivernois, Jean-François Dartigues, and Jean-François Warin

The effect of successful catheter ablation of overt accessory pathways on the incidence of atrial fibrillation (AF) was studied in 129 patients with ($n = 75$) or without ($n = 54$) previous documented AF. During a follow-up period of 35 ± 12 months (range 18 to 76), only 7 patients with

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previous spontaneous AF (9%) had recurrence at a mean of 10 months after ablation. Age, presence of structural heart disease, accessory pathway location, atrial refractory periods and accessory pathway anterograde conduction properties were not predictive of AF recurrence. Persistence of atrial vulnerability after ablation was associated with further recurrence of AF.

498

Efficacy of Intravenous Sotalol for Suppressing Inducibility of Supraventricular Tachycardias at Rest and During Isometric Exercise

Heikki V. Huikuri, M. Juhani Koistinen, and Juha T. Takkunen

The efficacy of intravenous sotalol for suppressing inducibility of supraventricular tachycardias (SVT) was studied in 30 patients with paroxysmal SVT. Orthodromic SVT was inducible in 14 patients, atrioventricular (AV) nodal reentrant SVT in 8, and intraatrial SVT in 8 before sotalol. Isometric handgrip exercise facilitated the inducibility of SVT in 8 patients who were noninducible at rest. After intravenous sotalol, 7 of 14 patients (50%) with orthodromic SVT, 8 of 8 (100%) with AV nodal SVT, and 8 of 8 (100%) with intraatrial SVT became noninducible into sustained SVT. Handgrip exercise facilitated the inducibility of only 3 nonsustained SVT runs after sotalol. Thus, sotalol is efficacious for suppressing SVT with AV nodal and intraatrial reentrant mechanisms, but less efficacious in patients with accessory AV pathway. The β-blocking and cellular antiarrhythmic effects of sotalol are not significantly reversed by exercise.

503

Conversion of Typical to "Atypical" Atrioventricular Nodal Reentrant Tachycardia After Radiofrequency Catheter Modification of the Atrioventricular Junction

Jonathan J. Langberg, Yoon-Nyun Kim, Rajiva Goyal, William Kou, Hugh Calkins, Joao Sousa, Rafel El-Atassi, and Fred Morady

Radiofrequency catheter modification of the atrioventricular junction was used to treat 88 patients with typical atrioventricular nodal reentry tachycardia (AVNRT). Nine of 81 (11%) patients successfully treated had new "atypical" AVNRT at follow-up electrophysiologic study. This arrhythmia was characterized by an RP > PR interval and was induced exclusively with ventricular pacing during isoproterenol infusion. Induction of atypical AVNRT was not predictive of arrhythmia recurrence, suggesting it should not be an indication for additional ablation sessions or long-term drug therapy.

509

Effect of Epinephrine on the Efficacy of the Internal Cardioverter-Defibrillator

João Sousa, William Kou, Hugh Calkins, Shimon Rosenheck, Alan Kadish, and Fred Morady

To evaluate the effect of sympathetic activation on the efficacy of the implantable cardioverter-defibrillator (ICD) in converting ventricular tachycardia (VT) or ventricular fibrillation (VF), 32 patients who re-

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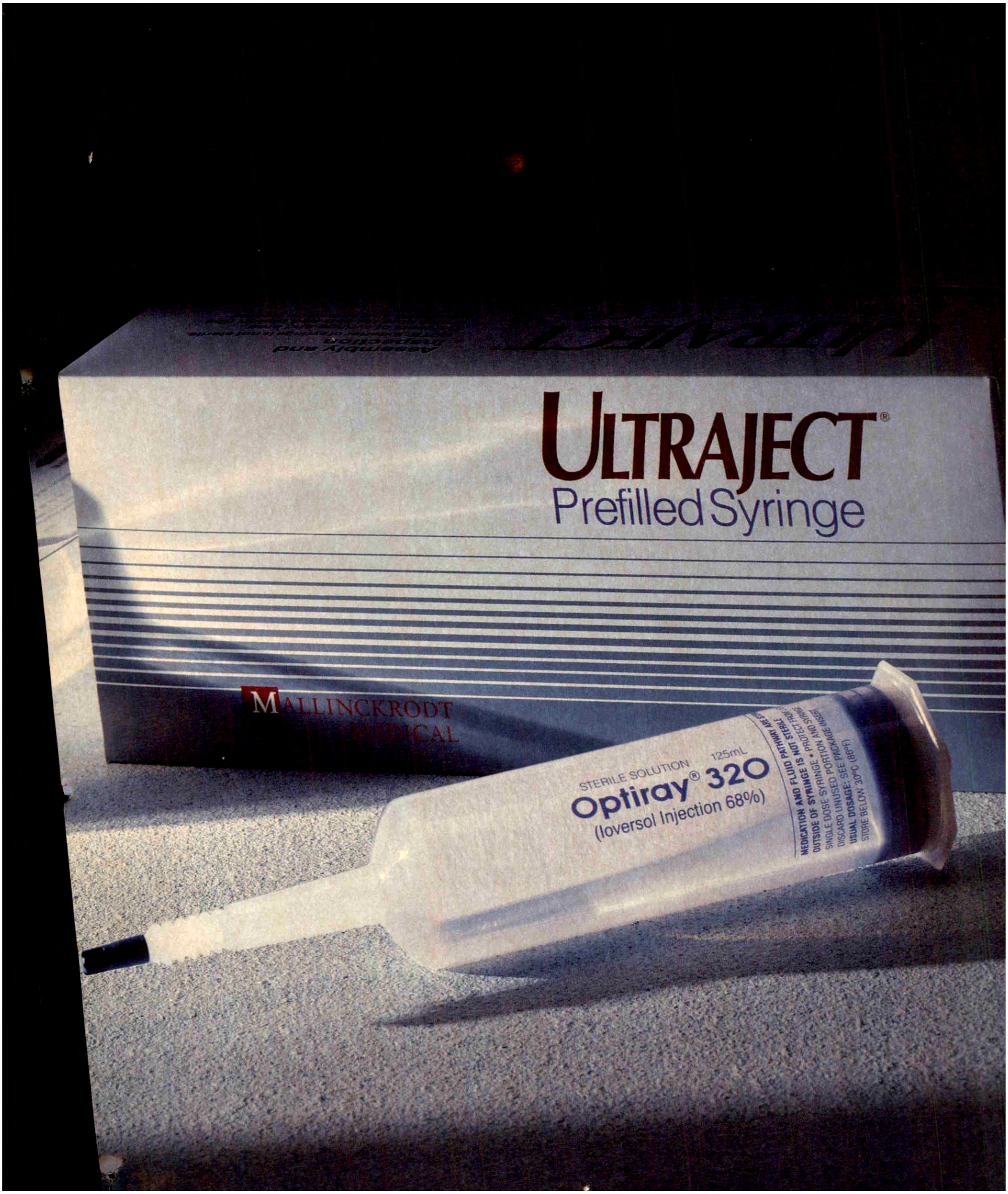
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ceived an ICD underwent 1-week postimplant ICD testing both before and after infusion of 25 (16 patients), or 50 (16 patients) ng/kg/min of epinephrine for 12 minutes. Among 16 patients with VT, epinephrine did not affect the efficacy of the ICD. Among 16 patients with VF, the first ICD discharge terminated VF in all patients in the baseline state, compared with 12 of 16 patients during epinephrine infusion ($p < 0.05$). In conclusion, physiologic increases in the plasma epinephrine concentration may increase the number and energy of shocks needed to terminate VF.

513

Clinical and Electrophysiologic Effects of Intravenous Dofetilide (UK-68,798), a New Class III Antiarrhythmic Drug, in Patients with Angina Pectoris

Martin L. Sedgwick, Henrik S. Rasmussen, and Stuart M. Cobbe

Dofetilide (UK-68,798) is a new class III antiarrhythmic agent. In animal experiments it selectively prolongs the refractory periods parallel to the action potential duration without any influence on upstroke velocity or conduction parameters. The present double-blind, placebo-controlled study was designed to show the effect of dofetilide on basic electrophysiologic parameters in patients with ischemic heart disease. Eighteen patients (aged 31 to 64 years) with symptoms of stable angina pectoris were randomly allocated to receive either placebo or 1 of 2 dose levels of dofetilide intravenously. Paired electrophysiologic variables were compared before and after administration. Both active dose levels produced significant prolongations ($p < 0.05$) of 10 to 23% in atrial effective refractory period, 6 to 16% in ventricular effective refractory period, and 11 to 15% in ventricular functional refractory period. Atrial functional refractory period was prolonged by 14 to 22% at the high-dose level ($p < 0.05$). No effect was observed on conduction parameters (PA, AH, HV, PR or QRS intervals), sinus cycle length or sinus node recovery.

SYSTEMIC HYPERTENSION

518

Safety of Pyridostigmine in Hypertensive Patients Receiving Beta Blockers

Michael Arad, Arie Roth, Julian Zelinger, Zehavit Zivner, Babeth Rabinowitz, and Jacob Atsmon

Pyridostigmine, a reversible inhibitor of acetylcholinesterase, was proposed for pretreatment of nerve gas poisoning. The cardiovascular effects of pyridostigmine in patients treated with β blockers were assessed. Eight hypertensive patients receiving β blockers were randomized to receive pyridostigmine (90 mg daily) or placebo. With each treatment, heart rate and blood pressure in the supine and standing positions were recorded every 2 hours, and 24-hour Holter monitoring and a symptom-limited exercise test were performed; plasma catecholamine levels were determined at rest and at peak exercise. Pyridostigmine did not induce any significant effect on heart rate, plasma catecholamine levels or blood pressure at rest. Systolic and diastolic blood pressures increased with exercise intensity ($p < 0.01$); however, a significantly lower diastolic blood

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pressure was observed with pyridostigmine (average decrease 5 mm Hg compared with placebo; $p < 0.01$). During the trial, no clinical adverse reactions were observed, confirming the relative safety of the combination of low-dose pyridostigmine with β-adrenergic blocking agents.

CONGESTIVE HEART FAILURE

523

Effects of Heart Failure on Baroreflex Control of Sympathetic Neural Activity

David W. Ferguson, William J. Berg, Paul J. Roach, Ron M. Oren,
and Allyn L. Mark, with the technical assistance of Joan S. Kempf

Whereas clinical heart failure is associated with impaired baroreflex control of heart rate, vascular resistance and plasma norepinephrine, recent studies in experimental heart failure suggest preserved baroreflex control of sympathetic nerve activity. Therefore, studies were performed to compare baroreflex control of efferent muscle sympathetic nerve activity (peroneal microneurography) in 10 normal human subjects and in 11 patients with moderate to severe heart failure. Compared with normal subjects, the sympathoinhibitory response to baroreceptor activation (phenylephrine) tended to be reduced and the sympathoexcitatory response to baroreceptor unloading (nitroprusside) was markedly blunted in the patients with heart failure.

532

Effect of Captopril on Cardiac Parasympathetic Activity in Chronic Cardiac Failure Secondary to Coronary Artery Disease

Andrew D. Flapan, James Nolan, James M. M. Neilson, and
David J. Ewing

Heart rate variability was measured from 24-hour ambulatory tape recordings on 2 separate occasions in 32 patients with chronic cardiac failure by counting the number of successive RR interval differences >50 ms. Group mean total 24-hour counts increased from 482 (range 23 to 6,120) to 1,033 (range 48 to 7,437) ($p = 0.002$) during treatment with captopril ($n = 20$). No significant changes were found in the subjects acting as controls ($n = 12$). Because the method used for measuring heart rate variability reflects cardiac parasympathetic activity, it is concluded that captopril increases cardiac parasympathetic activity in patients with chronic cardiac failure.

VALVULAR HEART DISEASE

537

Late (Two-Year) Follow-Up After Percutaneous Balloon Mitral Valvotomy

Peter C. Block, Igor F. Palacios, Elizabeth H. Block, E. Murat Tuzcu, and Brian Griffin

Studies comparing percutaneous balloon mitral valvotomy (PBMV) with closed and open surgical commissurotomy have shown comparable improvement early after PBMV. In a cohort of 41 patients, 24 ± 3 months of follow-up clinical evaluation, cardiac catheterization and echocardiographic studies are reported. At follow-up, 17 patients were New York Heart Association class I, 20 were class II, and 4 were class III. Mean follow-up mitral valve area by catheterization was 1.5 ± 0.1 cm^2, by planimetry 1.6 ± 0.1 and by Doppler halftime 1.7 ± 0.1 (all $p =$ not significant). In patients with more flexible, less calcified valves there was no trend toward restenosis. PBMV is effective therapy for selected patients with mitral stenosis at midterm follow-up. Cardiac catheterization data immediately after PBMV may yield an erroneously large mitral valve area owing to left-to-right shunting; planimetry by echocardiography may be more reliable.

MISCELLANEOUS

542

Reproducibility of Quantitative Backscatter Echocardiographic Imaging in Normal Subjects

John E. Stuhlmuller, David J. Skorton, Trudy L. Burns, Hewlett E. Melton, Jr., and Byron F. Vandenberg

Although cyclic backscatter variation is useful in differentiating normal from ischemic or myopathic myocardium, current methods of quantitative backscatter imaging include techniques with limited spatial and temporal sampling of backscatter. These methods provide either limited sampling of only 2 frames per cycle with the 2-dimensional technique or limited spatial sampling with the M-mode technique. We studied the reproducibility of these 2 approaches in 20 normal subjects, imaging them in separate sessions. There were no significant differences in group means on repeat measurements; however, repeat measurements in individual subjects were not reliably reproduced. Increased independent sampling and measurements from a backscatter waveform throughout the cardiac cycle may improve reproducibility of measurements.

547

Effects of Cardiac Transplantation on Ventilatory Response to Exercise

Kevin P. Marzo, John R. Wilson, and Donna M. Mancini

Patients with heart failure frequently exhibit an excessive ventilatory response to exercise. To investigate whether these ventilatory responses

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resolve after cardiac transplantation, 15 ambulatory patients with severe heart failure underwent exercise testing with measurement of respiratory gases before and 15 ± 6 months after transplantation. Ventilatory response was also measured in 7 control subjects. After transplantation, peak oxygen consumption increased from 11.8 ± 1.9 to 19.2 ± 3.1 ml/kg/min ($p < 0.001$), but remained significantly lower than in control subjects (33.4 ± 6.9 ml/kg/min; $p < 0.01$). Minute ventilation ($\dot{V}_E$) during exercise was significantly reduced after transplantation, but remained excessive compared with that in control subjects. Ventilation at a carbon dioxide production of 1 liter/min decreased significantly after cardiac transplantation (52.1 ± 7.9 to 38.8 ± 3.8 liters; $p < 0.01$), but remained elevated when contrasted with that in control subjects (31.4 ± 3.4 liters; $p < 0.05$). Ventilatory response to exercise is significantly improved after cardiac transplantation; however, $\dot{V}_E$ remains excessive. This may reflect an attenuated cardiac output response to exercise, abnormal intrapulmonary pressures or persistent deconditioning.

BRIEF REPORTS

554

Influence of Residual Blood Flow in the Infarct-Related Artery on Ventricular Tachycardia After Myocardial Infarction

Leslie A. Saxon, C. Todd Sherman, William G. Stevenson, Lawrence A. Yeatman, and Isaac Wiener

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Prevalence of Silent Myocardial Ischemia Detected by 24-Hour Ambulatory Electrocardiography, and Its Association with New Coronary Events at 40-Month Follow-Up in Elderly Diabetic and Nondiabetic Patients with Coronary Artery Disease

Wilbert S. Aronow, Anthony D. Mercando, and Stanley Epstein

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Frequency of Ventricular Ectopic Activity in Isolated Systolic Systemic Hypertension

John B. Kostis, Clifton R. Lacy, Daniel M. Shindler, Nemat O. Borhani, W. Dallas Hall, Alan C. Wilson, Susan Krieger, and Sandra Chelton

560

Detection of Patent Foramen Ovale by Transcranial Contrast Doppler Ultrasound

Ronald Karnik, Claudia Stöllberger, Andreas Valentin, Walther-Benedikt Winkler, and Jörg Slany

562

Estimation of Pulmonary Arterial Wedge Pressure by Pulsed Doppler Echocardiography and Phonocardiography

Marvin Berger, Matt Bach, Susan R. Hecht, and Andrew Van Tosh

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In hypertension, CAPOTEN may be used as initial therapy (25 mg bid or tid) for patients with normal renal function, in whom the risk of neutropenia/agranulocytosis is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

In heart failure, CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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Richard Lower (1631–1691): A Pioneer of Cardiologic Research
Andrew J. Larner

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Assessment by Echocardiogram of Left Ventricular Diastolic Function in Healthy Subjects Using the Atrioventricular Plane Displacement
Mahbubul Alam and Christer Höglund

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Cytologic Analysis of Pericardial Effusion Complicating Extracardiac Malignancy
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READERS' COMMENTS

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Lipoprotein (a) is Not a Risk Factor for Restenosis After Percutaneous Transluminal Coronary Angioplasty
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Seismocardiography is Not a New Term
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Single Inoue Balloon Catheter Versus Double Mansfield Balloon Catheter Techniques in Percutaneous Balloon Mitral Valvuloplasty
Tsung O. Cheng

Correction

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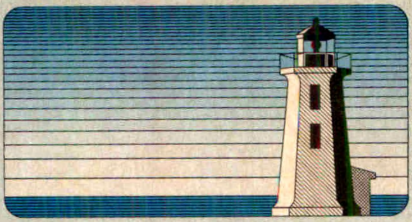

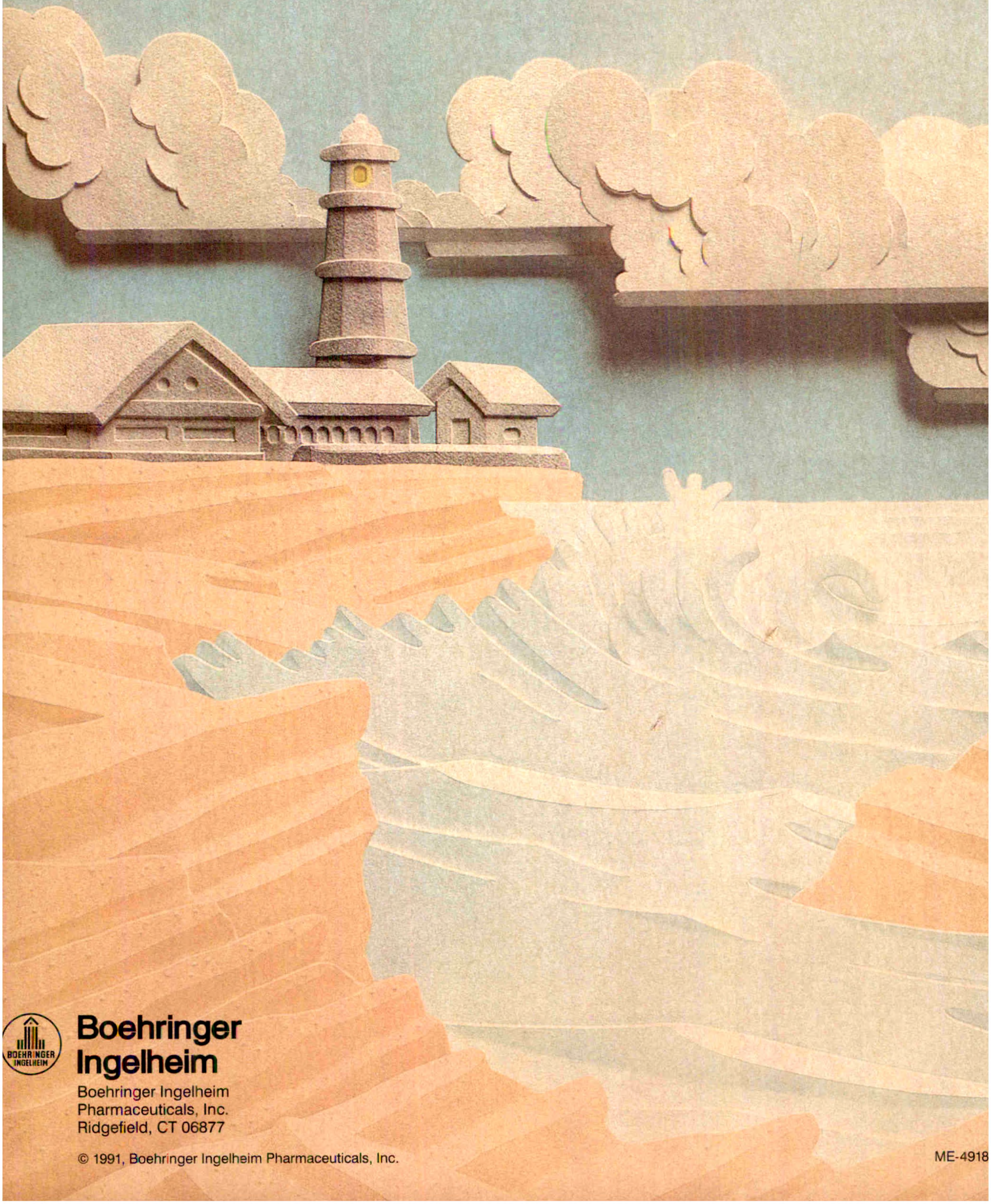

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PREVENTIVE CARDIOLOGY

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Role of Water-Soluble Dietary Fiber in the Management of Elevated Plasma Cholesterol in Healthy Subjects

William L. Haskell, PhD, Gene A. Spiller, PhD, Christopher D. Jensen, RD, Brenda K. Ellis, MS, RN, and Joan E. Gates, RD, MPH

Guidelines for the use of water-soluble dietary fibers (WSDF) in the dietary management of elevated plasma cholesterol are not well-established. Consequently, 4 studies were conducted to explore the plasma lipid-lowering effects of a variety of WSDF. Studies were randomized, double-blind, placebo-controlled trials involving healthy men and women (plasma cholesterol >5.17 mmol/liter; >200 mg/dl). Study duration ranged from 4 to 12 weeks. The WSDF acacia gum yields a low viscosity, palatable beverage when mixed in water. However, despite its WSDF classification, acacia gum consumed for 4 weeks as the sole WSDF source (15 g of WSDF/day) or primary source in a WSDF mixture (17.2 g of WSDF/day; 56% derived from acacia gum) did not produce a significant lipid-lowering effect versus placebo. When 15 g of WSDF/day consisting of psyllium husk, pectin, and guar and locust bean gums (medium viscosity) was consumed for 4 weeks, significant reductions in cholesterol resulted (total cholesterol 8.3%, low-density lipoprotein cholesterol 12.4%; p <0.001) that were comparable to changes achieved with 10 g of WSDF/day from high-viscosity guar gum. The magnitude of the lipid-lowering effect was related to intake of WSDF ranging from 5 to 15 g/day (low-density lipoprotein cholesterol +0.8% [placebo], −5.6% [5 g/day], −6.8% [10 g/day], −14.9% [15 g/day]; p <0.01 for trend). The effects of WSDF on plasma lipids were similar for men and women. A diet rich in selected WSDF may be a useful adjunct to the dietary management of elevated plasma cholesterol.

(Am J Cardiol 1992;69:433–439)

Elevated plasma total and low-density lipoprotein (LDL) cholesterols are major risk factors for coronary heart disease,[1] and their reduction in high-risk men leads to a lower incidence of fatal and nonfatal cardiac events.[2] Using the National Cholesterol Education Program (NCEP) criteria, approximately 57% of adult Americans have borderline high or high total cholesterol concentrations (>5.17 mmol/liter or >200 mg/dl) and are candidates for cholesterol lowering.[3] The NCEP-suggested treatment for elevated plasma cholesterol begins with dietary management.[4] The general aim of these dietary recommendations is to lower total and LDL cholesterol concentrations by reducing the intake of saturated fatty acids and cholesterol, and to promote weight loss in persons who are overweight by eliminating excess calories. A nutritionally adequate diet containing a diversity of foods is recommended, with emphasis placed on the increased consumption of grains, fruits and vegetables.

The addition of various water-soluble dietary fibers (WSDF) such as guar gum, psyllium husk or oat products to the typical American diet or a diet somewhat lower in fat (e.g., the American Heart Association step-one diet) tends to lower plasma cholesterol concentrations.[5-7] However, the role of WSDF as a component of the dietary management of elevated cholesterol is not well-established. For example, the amount of food needed in the case of oat products, and the viscosity and taste characteristics of guar gum and psyllium husk preparations serve as potential deterrents to regular consumption of these foods. In addition, very little is known about the cholesterol-lowering efficacy of other types or combinations of WSDF. The objective of the research reported here was to explore the cholesterol-lowering efficacy of different types, combinations and amounts of WSDF.

METHODS

Overview: These studies were conducted to answer specific questions regarding the influence of WSDF intake on plasma lipid and lipoprotein concentrations in generally healthy men and women. Subjects were recruited using articles and advertisements in local newspapers, notices placed in large corporations and referral by private physicians. To be eligible, subjects had to be

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From Stanford Center for Research in Disease Prevention, Stanford University School of Medicine, Stanford, Health Research and Studies Center, Los Altos, and Shaklee U.S., Inc., a Division of Yamanouchi Pharmaceutical Corporation, San Francisco, California. This research was supported by Shaklee U.S., Inc., a Division of Yamanouchi Pharmaceuticals Corporation, San Francisco, California. Manuscript received July 11, 1991; revised manuscript received and accepted October 22, 1991.

Address for reprints: William L. Haskell, PhD, Stanford Center for Research in Disease Prevention, Stanford University School of Medicine, 730 Welch Road, Suite B, Palo Alto, California 94304.

TABLE I Water-Soluble Dietary Fiber Composition of Products Used in Each Study

	Study 1	Study 2	Study 3 WSDF Mix	Study 3 Guar Gum	Study 4		
Servings/day	3	3	3	3	1	2	3
WSDF source (g/day)							
Pectin	—	—	3.9	1	1.3	2.6	3.9
Acacia gum	9.7	15	—	—	—	—	—
Psyllium husk	4.9	—	6.3	—	2.1	4.2	6.3
Guar gum	2.6	—	3.3	10	1.1	2.2	3.3
Locust bean gum	—	—	1.5	—	0.5	1	1.5
Total WSDF (g/day)	17.2	15	15	10	5	10	15
Viscosity (cp)*							
4 minutes	10.5	6.7	110	1,000	110	110	110
6 minutes	12.5	6.5	145	2,500	145	145	145
10 minutes	16.5	6.5	225	10,000	225	225	225

*Viscosity measured at 4, 6, and 10 minutes using a Brookfield Viscosimeter (Brookfield Instrument Company, Stoughton, MA; model LVTDV).
WSDF = water-soluble dietary fiber.

aged 20 to 75 years, have plasma cholesterol concentrations >5.17 mmol/liter (>200 mg/dl) and plasma triglycerides <3.95 mmol/liter (<350 mg/dl), not be on any lipid-lowering medications or dietary fiber supplementation, have fasting glucose <6.6 mmol/liter (<120 mg/dl), no history of gastrointestinal diseases or evidence of such diseases on medical examination, normal liver function tests, no history or evidence of any disease that may influence lipoprotein metabolism (thyroid, cancer and so forth), and <130% ideal body weight (1959 Metropolitan Life Insurance tables). Persons were eligible who were receiving antihypertensive medications (blood pressure stable at <160/95 mm Hg), oral contraceptives or estrogen replacement therapy if they had been on a stable dose for ≥6 months and had no plans to change. All studies were approved by a committee on the use of human subjects in research, and written informed consent was obtained from each subject after the study protocol had been explained. No subject participated in >1 study. The studies were initiated consecutively in the order presented.

Treatments: The dietary fiber mixtures, which provided predominantly WSDF, were prepared as powders in a carbohydrate base (approximately 15 g of fructose per serving) for palatability (Table I). In studies 1, 2 and 4, the placebo products were also prepared as powders with only the carbohydrate fraction present, so that equal calories (approximately 70 calories/serving) were provided to both the treatment and placebo groups. The viscosity of each WSDF mixture and placebo was measured each minute for 10 minutes after 1 serving of powder was quickly suspended in 10 oz of cold water, shaken and immediately transferred to a drinking glass. We arbitrarily defined acacia gum as low viscosity, the WSDF mixture as medium viscosity, and guar gum as high viscosity (Table I).

In study 3, a mixture of sources of WSDF (15 g of WSDF, 70 calories/serving), and a positive control (guar gum) were administered in a crossover design. Ten g of WSDF from high-viscosity guar gum (cyamopsis tetragonolobus) were administered daily. The 10 g/day dose was selected for palatability and because previous research had shown guar gum in this range to be cholesterol-lowering.[7-9] The guar gum was formulated in a base of artificial sweetener so that subjects in this group did not receive added calories with their fiber supplement. In each study, subjects were instructed to mix their treatment powders in an appropriate volume of water (6 to 10 oz) and to consume the beverages with their major meals. In addition, all subjects were instructed to maintain their typical eating and physical activity patterns.

Measurements: Measurements were obtained using similar protocols for each study. Any differences are stated in the description of the specific study. All subjects completed a screening medical history, including medications, and if their plasma total cholesterol and triglycerides were not known, a screening lipid panel was performed. Eligible subjects underwent a cardiovascular-oriented physical examination, with measurements of body height and weight, and blood pressure. Venous blood samples were obtained after a 12- to 14-hour fast on 2 separate days within a period of 8 days for analysis of plasma lipids and lipoproteins. The values obtained at these 2 visits were averaged and used as the baseline values for each subject. Two 10 ml blood samples were obtained from the antecubital vein into vacutainer tubes containing 15 mg of ethylene diaminetetraacetic acid. Each sample was kept cool and centrifuged to obtain plasma, and the plasma was kept refrigerated until analyzed on the day after obtaining the blood sample.

High-density lipoprotein (HDL) was separated from the plasma by a precipitation procedure using dextran sulfate and magnesium chloride. Cholesterol in the remaining plasma and in the separated HDL fraction was measured by an enzymatic procedure[10] on a Spectrum Analyzer (Abbott Laboratories, North Chicago, IL). Triglycerides corrected for the glycerol blank were analyzed by an enzymatic ultraviolet procedure on the same Spectrum Analyzer. These analytical procedures were standardized and met the performance requirements of the Lipoprotein Standardization Program of the Centers for Disease Control (Atlanta, GA), and are traceable to the National Reference System for Cholesterol. Very low-density lipoprotein cholesterol was estimated by dividing the triglyceride value by 5. LDL cholesterol was estimated according to the Friedewald method.[11]

Randomization and follow-up: In each study, subjects were randomized to treatment or placebo groups after all baseline data were collected. All studies were double-blinded. Follow-up evaluations were conducted at specific intervals using the same procedures as at baseline.

Data analysis: To determine if differences between groups at baseline or if the changes in the treatment groups compared with those in the placebo groups were significant, 2 sample *t* tests were used for studies with 2 groups (studies 1, 2 and 3), and analysis of variance for study 4, which had 4 groups. Gender differences and treatment effects were determined using 2-way analysis of variance with gender and treatment as the main factors. Significance was set at $p < 0.05$.

RESULTS

Study 1: EVALUATION OF A WATER-SOLUBLE DIETARY FIBER MIXTURE CONTAINING ACACIA GUM AS THE MAJOR SOURCE OF DIETARY FIBER: Psyllium husk (plantago psyllium) and guar gum, consumed independently, lower plasma cholesterol concentrations.[5,7-9] However, their viscous nature when mixed in water can be a deterrent to palatability and can adversely affect compliance when a regimen of regular dietary intake is required. Acacia gum (*acacia senegal or verak*) is a WSDF source that is substantially lower in viscosity when mixed with water (Table I). This study was conducted to determine the cholesterol-lowering effectiveness of consuming approximately 17 g/day of WSDF from a mixture of dietary fiber sources, with the major WSDF source being acacia gum (56%) and the remainder from psyllium husk and guar gum.

DESIGN: After baseline evaluations, subjects were randomized to a double-blind, placebo-controlled trial of 12 weeks' duration. In all, 62 subjects (30 men and 32 women, mean age 57.4 ± 10.2 years, plasma cholesterol concentrations between 5.17 and 7.35 mmol/liter) met the eligibility criteria and were randomly assigned to 1 of 2 groups: a WSDF group (n = 32) that was prescribed 17.2 g/day of WSDF from a mixture of dietary fiber sources, or a placebo group (n = 30) (Table I). Adherence and side effects were monitored using a diary. Diaries were completed daily and returned every 2 weeks for review by project staff. At 6 and 12 weeks subjects completed a follow-up medical history and exam, and a fasting blood sample was obtained for measurement of plasma lipids. At baseline and 12 weeks subjects completed a Block-type food frequency questionnaire.[12]

RESULTS: Of the 62 subjects randomized to treatment or placebo, 58 completed the 12-week trial and all evaluation sessions. Dropouts included 1 patient in the placebo group (disliked taste of product) and 3 in the treatment group (diagnosis of intestinal parasite unrelated to product use [1]; gastrointestinal side effects [1]; study time contraints [1]). Side effects reported were mainly transient abdominal bloating (placebo 8%; WSDF 26%) and increased stool frequency (placebo 12%; WSDF 19%) and flatus (placebo 10%; WSDF 24%), and were generally minor for both groups. Assessment of daily logs indicated 94% adherence in the treatment group, and 97% in the placebo group (number of servings taken/prescribed × 100 = % adherence).

TABLE II Study 1: Plasma Lipid Concentrations (mmol/liter: mean ± SD) and Body Weights at Baseline and in Response to a Water-Soluble Dietary Fiber Mixture of Acacia Gum, Psyllium Husk and Guar Gum (n = 29), and to Placebo (n = 29)

	Baseline	6 Weeks	12 Weeks	Percent Change*
Total cholesterol				
Placebo	6.05 ± 0.47	6.05 ± 0.65	6.02 ± 0.47	−0.5
Fiber mixture	5.97 ± 0.82	5.86 ± 0.91	5.79 ± 0.88	−3.0
LDL cholesterol				
Placebo	3.86 ± 0.57	3.74 ± 0.75	3.71 ± 0.62	−3.9
Fiber mixture	4.01 ± 0.67	3.88 ± 0.73	3.78 ± 0.73	−5.7
HDL cholesterol				
Placebo	1.54 ± 0.44	1.57 ± 0.44	1.46 ± 0.41	−5.2
Fiber mixture	1.47 ± 0.47	1.41 ± 0.31	1.39 ± 0.44	−5.4
Triglycerides				
Placebo	1.44 ± 0.64	1.57 ± 0.70	1.68 ± 0.73	+16.7
Fiber mixture	1.36 ± 0.61	1.53 ± 0.73	1.52 ± 0.70	+11.8
Body weight (kg)				
Placebo	72.5 ± 14.6	72.6 ± 15.0	73.3 ± 14.9	+1.1
Fiber mixture	71.6 ± 13.9	71.7 ± 14.1	71.9 ± 14.7	+0.4

*Percent change for mean values from baseline to 12 weeks. No changes within or between groups from baseline to 6 or 12 weeks were statistically significant ($p < 0.05$).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

The baseline (mean of 2 values) and treatment (at 6 and 12 weeks) values for plasma lipids and body weight are listed in Table II. At baseline, mean values for all lipid measurements were similar for the 2 groups. During the treatment period there were no significant changes in plasma lipid concentrations within or between the groups. The interaction of treatment by gender was also tested, and in no case were the changes statistically significant. Over the 12 weeks there were no significant changes in body weight or reported dietary intake of calories or major nutrients for either group.

Study 2: THE EFFECTS OF ACACIA GUM ON PLASMA LIPOPROTEIN CONCENTRATIONS: Acacia gum was a major WSDF source in the mixture of fibers that did not significantly influence plasma cholesterol concentrations in study 1. Acacia gum differs markedly in chemical structure and viscosity when mixed in water from that of other well-established WSDF sources, such as guar gum,[12] and has not been thoroughly studied for its cholesterol-lowering properties. Consequently, we evaluated acacia gum independent of other WSDF sources for its cholesterol-lowering effects.

DESIGN: In all, 42 subjects (21 men and 21 women, mean age 56.4 ± 9.4 years) were randomized to placebo (n = 22) or 15 g/day of WSDF from acacia gum (n = 22) for 1 month. Lipid measurements were repeated after 3 and 4 weeks of treatment. Means of the values at weeks 3 and 4 were used as the treatment values in the analysis. A 3-day diet record was completed by

TABLE III Study 2: Plasma Lipid Concentrations (mmol/liter; mean ± SD) and Body Weights at Baseline and in Response to Acacia Gum and Placebo

Plasma Lipid	Placebo (n = 21)		Acacia Gum (n = 21)	
	Baseline	4 Weeks	Baseline	4 Weeks
Total cholesterol	6.83 ± 0.65	6.97 ± 0.60	6.89 ± 0.85	6.85 ± 0.91
Change		+0.14 ± 0.44		−0.04 ± 0.45
% change		+1.9%		−0.4%
LDL cholesterol	5.15 ± 0.70	5.31 ± 0.61	5.02 ± 0.84	5.04 ± 0.90
Change		+0.16 ± 0.37		+0.02 ± 0.35
% change		+3.3%		0.0%
HDL cholesterol	1.43 ± 0.40	1.35 ± 0.40	1.55 ± 0.48	1.49 ± 0.43
Change		−0.07 ± 0.12		−0.06 ± 0.17
% change		−5.4%		−3.9%
Triglyceride	1.48 ± 0.59	1.50 ± 0.59	1.49 ± 0.79	1.57 ± 0.85
Change		+0.25 ± 0.52		+0.01 ± 0.64
% change		+16.6%		+0.7%
Body weight (kg)	70.9 ± 12.7	70.9 ± 12.3	71.8 ± 12.3	72.3 ± 70.9
Change		0		0.7 ± 0.92
% change		0%		+0.9%

No changes within or between groups from baseline to 4 weeks were statistically significant ($p < 0.05$).
Abbreviations as in Table II.

subjects during the baseline period and fourth week of treatment. Adherence and side-effects were monitored by weekly phone calls or office visits.

RESULTS: Of the 42 subjects randomized, 40 completed the study. One subject in each group did not complete the study owing to flu-like symptoms considered unrelated to participation in the study. The consumption of placebo or 15 g/day of WSDF from low-viscosity acacia gum produced no significant changes in plasma total, LDL and HDL cholesterols, and triglyceride concentrations and body weight during the 4 weeks of treatment, either within or between the 2 groups (Table III). In no case was the interaction of treatment by gender statistically significant for the changes in lipid concentrations. During the 4 weeks there were no significant changes in body weight or reported dietary intake. No medically significant side effects were reported. Mild transient side effects such as bloating, increased stool frequency and flatulence were noted in 9% of the placebo group and in 36% of the acacia gum group. Adherence was >99% in both groups

TABLE IV Study 3: Plasma Lipid Concentrations (mmol/liter; mean ± SD) and Body Weights at Baseline and in Response to Guar Gum and a Water-Soluble Dietary Fiber Mixture

Plasma Lipid	Baseline	After Treatment (4 weeks)	
		Guar Gum (n = 14)	Fiber Mixture (n = 14)
Total cholesterol	6.44 ± 0.56	5.82 ± 0.63	5.92 ± 0.62
Change		−0.62 ± 0.44*	−0.54 ± 0.38*
% change		−9.7%	−8.3%
LDL cholesterol	4.76 ± 0.49	4.20 ± 0.53	4.28 ± 0.61
Change		−0.55 ± 0.42*	−0.54 ± 0.38*
% change		−13.6%	−12.4%
HDL cholesterol	1.39 ± 0.24	1.30 ± 0.27	1.32 ± 0.22
Change		−0.09 ± 0.12†	−0.08 ± 0.11†
% change		−6.5%	−5.9%
Triglyceride	1.40 ± 0.45	1.54 ± 0.68	1.59 ± 0.53
Change		+0.14 ± 0.53	+0.22 ± 0.56
% change		+9.7%	+15.3%
Body weight (kg)	73.4 ± 12.7	73.6 ± 13.6	74.0 ± 13.1
Change		+0.2 ± 0.7	+0.6 ± 1.1
% change		+0.3%	+0.8%

*Mean changes from baseline were statistically significant at $p < 0.01$; †mean changes from baseline were statistically significant at $p < 0.05$.
Abbreviations as in Table II.

Study 3: WATER-SOLUBLE DIETARY FIBER MIXTURE WITH LOCUST BEAN GUM AND PECTIN SUBSTITUTED FOR ACACIA GUM: Because locust bean gum (*ceratonia siliqua*) has a chemical structure similar to guar gum,[13] and high-methoxyl pectin has been shown to lower plasma cholesterol concentrations,[14–18] these 2 WSDF sources were incorporated into a WSDF mixture in lieu of acacia gum (Table I) and evaluated in an 8-week crossover study design using guar gum as a positive control.

DESIGN: After baseline evaluations, 16 subjects (7 men and 9 women, mean age 52.5 ± 10.8 years) were randomized to a positive control (10 g/day of WSDF from high-viscosity guar gum) or 15 g of WSDF from a mixture of 4 fiber sources (Table I). Subjects were instructed to take the guar gum immediately before their 2 major meals of the day. Lipid measurements were repeated after 3 and 4 weeks of treatment. After 4 weeks subjects were crossed over to the other treatment with measurements repeated again after 3 and 4 weeks. Means of the values at weeks 3 and 4 were used as the treatment values in the analysis. A 3-day diet record was completed by all subjects at baseline and at the end of each treatment period. Adherence and side effects were monitored by weekly phone calls or office visits.

RESULTS: Both WSDF products yielded significant reductions from baseline in total ($p < 0.001$), LDL ($p < 0.001$) and HDL ($p < 0.01$) cholesterols (Table IV). Although somewhat elevated, the changes in triglycerides were not significantly different from baseline values. There were no statistically significant differences in any of the plasma lipid changes between the 2 treatment groups, nor was there a significant interaction of treatment by gender. Body weight and reported dietary intake of calories or major nutrients did not significantly change in either group at either time period. One

TABLE V Study 4: Plasma Lipid Concentrations (mmol/liter; mean ± SD) at Baseline and in Response to Placebo or 5, 10 and 15 g/Day of a Water-Soluble Dietary Fiber Mixture Consisting of Pectin, Psyllium Husk, and Guar and Locust Bean Gums

	Placebo (n = 11)		Fiber Mixture (5 g/day) (n = 12)	
Plasma Lipid	Baseline	4 Weeks	Baseline	4 Weeks
Total cholesterol	6.76 ± 0.88	6.78 ± 0.88	6.59 ± 0.78	6.25 ± 0.96
Change		+0.02 ± 0.55		−0.34 ± 0.42
% change		+0.3%		−5.2%
LDL cholesterol	4.75 ± 0.77	4.79 ± 0.73	4.81 ± 0.76	4.54 ± 0.86
Change		+0.04 ± 0.47		−0.27 ± 0.37
% change		+0.8%		−5.6%
HDL cholesterol	1.72 ± 0.33	1.61 ± 0.34	1.46 ± 0.41	1.40 ± 0.44
Change		−0.11 ± 0.13		−0.06 ± 0.10
% change		−6.4%		−4.1%
Triglyceride	1.28 ± 0.80	1.59 ± 1.38	1.64 ± 0.70	1.57 ± 0.83
Change		+0.31 ± 0.68		−0.07 ± 0.47
% change		+24.2%		−4.3%
Body weight (kg)	71.3 ± 16.8	71.4 ± 16.8	69.0 ± 14.1	68.2
Change		−0.4 ± .89		−0.8 ± 2.1
% change		−0.5%		−1.2%
	Fiber Mixture (10 g/day) (n = 11)		Fiber Mixture (15 g/day) (n = 12)	
Total cholesterol	6.70 ± 0.82	6.37 ± 0.75	7.12 ± 1.17	6.25 ± 1.12
Change		−0.33 ± 0.49		−0.87 ± 0.51*
% change		−4.9%		−12.2%
LDL cholesterol	4.83 ± 0.71	4.50 ± 0.64	5.44 ± 1.09	4.63 ± 0.98*
Change		−0.33 ± 0.43		−0.81 ± 0.50
% change		−6.8%		−14.9%
HDL cholesterol	1.58 ± 0.49	1.61 ± 0.46	1.38 ± 0.33	1.25 ± 0.27
Change		−0.04 ± 0.08*		−0.13 ± 0.13
% change		−2.5%		−9.4%
Triglyceride	1.50 ± 0.75	1.32 ± 0.72	1.55 ± 0.57	1.87 ± 0.78
Change		−0.18 ± 0.49		+0.32 ± 0.28
% change		−12.0%		+20.6%
Body weight (kg)	72.7 ± 14.5	72.7 ± 14.1	73.6 ± 9.09	73.6 ± 9.04
Change		0		0
% change		0%		0%

*Statistically significant at p < 0.05 from placebo control.
Abbreviations as in Table II.

subject in each group did not complete the study: 1 in the guar gum group owing to personal reasons, and 1 in the WSDF mixture group owing to nausea and headaches after 4 days in the study. Adherence to the treatment regimens was 98% in the guar gum group, and 99% in the WSDF mixture group. Side effects included abdominal bloating, and increased stool frequency and flatulence, and were mild in 72% of subjects on guar gum and in 29% on the WSDF mixture. Moderate intensity bloating or gas occurred in 2% of subjects on guar gum, but in none on the WSDF mixture.

Study 4: DOSE EFFECTS OF A WATER-SOLUBLE DIETARY FIBER MIXTURE: Having established in study 3 that a medium-viscosity WSDF mixture providing a total daily dose of 15 g of WSDF could significantly lower total and LDL cholesterol concentrations, a dose response study was conducted.

DESIGN: Forty-nine hypercholesterolemic subjects (19 men and 30 women, mean age 56.3 ± 9.5 years) were randomly assigned either to placebo (n = 12) or to 5 (n = 12), 10 (n = 13) or 15 (n = 12) g/day of WSDF mixture for 1 month. Subjects were instructed to consume their WSDF with their largest meals; 1, 2 or 3 times daily depending on the dose (5, 10 or 15 g/day). Lipid measurements were repeated after 3 and 4 weeks of treatment, with the means of these 2 values used as treatment values in the analysis. A 3-day diet record was completed by subjects during the baseline period and during the fourth week of treatment. Adherence and side effects were monitored by weekly phone calls or office visits.

RESULTS: The changes in plasma lipids elicited by the 3 WSDF doses were compared with those in the placebo group (Table V). The decreases in total (12.2%) and LDL (14.9%) cholesterols observed for the 15 g/day group were significant compared with those in the placebo group (p <0.05). In addition, there was a significant trend for greater total and LDL cholesterol decreases with increasing WSDF doses from 5 to 15 g/day (p <0.01). HDL cholesterol concentrations decreased in all groups, with the changes in the placebo (6.4%) and 15 g/day of WSDF (9.4%) groups being greater than those in the 10 g/day group (2.5%). The plasma triglyceride response was variable, with the increase in the placebo group (24.2%) being significantly different from the decreases in the 5 (−4.3%) and 10

TABLE VI Effects of Various Water-Soluble Dietary Fibers on Plasma Cholesterol Concentration

Study	WSDF Source	Dose (g/day)	Duration (weeks)	Change (%)	TCb	TCf*
Jenkins[19]	Guar gum	15	2	−11	8.91	7.96
Bosello[20]	Guar gum	16	4	−12	7.83	6.86
Aro[21]	Guar gum	15	6	−15	8.59	7.27
Jenkins[22]	Guar gum	13	8	−13	−1.20	
Penagini[8]	Guar gum	11	2	−16	4.81	4.03
Khan[7]	Guar gum	9	4	−17	4.65	3.90
Smith[23]	Guar gum	20	3	−14	5.46	4.68
Superko[9]	Guar gum	15	4	−10	6.23	5.58
Abraham[24]	Psyllium	21	3	−16	4.83	4.06
Bell[6]	Psyllium	10	8	− 4	5.90	5.65
Anderson[5]	Psyllium	10	8	−15	6.39	5.45
Vargo[14]	Pectin	15	3	−18	5.32	4.34
Kay[15]	Pectin	15	3	−15	5.79	4.91
Zavoral[25]	Locust bean gum	8–30	8	−17	8.11	6.77
Behall[26]	Locust bean gum	24	4	−14	5.06	4.37
Behall[26]	Karaya gum	24	4	−10	5.06	4.57

*Values are group means in mmol/liter (to convert to mg/dl, multiply by 38.67).
TCb = cholesterol concentration at baseline; TCf = cholesterol concentration after treatment; WSDF = water-soluble dietary fiber.

(−12.0%) g/day groups. However, no systematic pattern of significant changes related to fiber dose was observed for either HDL cholesterol or triglycerides. In no case was the interaction of treatment by gender statistically significant for any of the changes. Body weight and reported dietary intake of calories and major nutrients did not significantly change in any of the groups. Adherence in each group was >99% (total missed doses were 5 g/day = 4, 10 g/day = 1; 15 g/day = 10; placebo = 10). Three subjects did not complete the study: 1 in the 10 g/day group owing to cramps and diarrhea, 1 in the 15 g/day group owing to nausea and intestinal cramps, and 1 in the 5 g/day group owing to incomplete data collection. Other side effects reported were generally minor and transient, including abdominal bloating, and increased stool frequency or flatulence, and were reported by 36% of placebo subjects and by 18, 64 and 50% of subjects in the 5, 10 and 15 g/day groups, respectively. In 8% of the 15 g/day subjects, moderate intensity gastric side effects were reported.

DISCUSSION

The lack of a significant effect on plasma lipoproteins seen when acacia gum was administered in beverage form, either as the major source of WSDF (study 1) or in isolation (study 2), is in contrast to the results of similarly designed studies of other types of WSDF administered in similar amounts, which have exhibited significant hypocholesterolemic effects (Table VI).

We know of only 2 published studies that examined the effect of acacia gum on plasma cholesterol. In 1 of these studies,[27] 5 men were administered 25 g of acacia gum in beverage form once daily for 3 weeks, which elicited a 6.3% decline in serum cholesterol concentration. In the other study,[28] a total of 7 men and women were administered a total of 30 g/day of acacia gum in the form of a lentil soup dish consumed twice daily, which caused a 10.4% decline in serum cholesterol concentration. In both of these studies, substantially larger amounts of acacia gum were administered in fewer divided doses than in the current study, which could account for its hypocholesterolemic effects. However, it should be noted that neither study included a control group, and such large amounts of added dietary fiber may lead to other changes in the diet that could lower total cholesterol. In addition, acacia gum can be obtained from many different types of acacia tree, and its cholesterol-lowering properties may vary depending on the type of tree used, the growing conditions and how the acacia gum is processed.

A number of mechanisms have been proposed to explain the cholesterol-lowering properties apparent with some WSDF sources. These effects include: (1) a binding of WSDF with bile acids or other lipids, or both, which may interfere with micelle formation in the proximal small intestine, leading to alterations in the quantity of cholesterol or fatty acids absorbed; (2) an increase in fecal excretion of bile acids that may ultimately affect hepatic synthesis of lipoproteins; and (3) fermentation of WSDF by colonic bacteria, whereupon formed gases and short-chain fatty acids may be absorbed into the portal vein and ultimately impair hepatic cholesterol synthesis.[29] Although the exact mechanisms remain unclear, it is possible that the physical-chemical structure of WSDF may be an important determinant of its cholesterol-lowering ability. Guar gum, a well-established hypocholesterolemic WSDF,[7-9,19-23] is a galactomannan derived from the guar bean. Acacia gum, a polymer of arabinose, rhamnose, galactose and glucuronic acid, is a tree exudate. Physical-chemical differences, such as viscosity, may account for differences in cholesterol-lowering properties. For example, the viscosity at 4, 6 and 10 minutes was significantly lower for the WSDF mix with acacia gum (10.5, 12.5 and 16.5 centipoises) than that for the mix with psyllium seed husk, guar and locust bean gums, and pectin (110, 145 and 225 centipoises, respectively).

When acacia gum was removed from the WSDF mixture and replaced by high-methoxyl–type pectin and locust bean gum in study 3, the combination of WSDF elicited a cholesterol-lowering effect similar to that of high-viscosity guar gum. Similar effects were seen despite a large difference in viscosity. It is possible that there is a threshold viscosity above which additional cholesterol-lowering benefits are minimal.

In examining the relation of dose of WSDF mixture to plasma lipid response (study 4), there was a significant association between fiber intake and mean plasma total and LDL cholesterol reduction, with the largest and most consistent reductions being observed with the 15 g/day dose. These findings appear to be in agreement with results of the only 2 published dose-response WSDF studies in humans that we have found, 1 of which showed that 6, 8 and 10 g of pectin administered daily for 4 weeks yielded a significant association between increasing dose and serum total cholesterol decline,[30] and the second showing that increasing intakes of oat bran cereal (25, 56 and 34 g/day) yielded an inverse effect on serum LDL concentrations.[31]

The finding that decreases in total cholesterol are largely due to reductions in LDL cholesterol (studies 3 and 4), and the lack of any systematic pattern of change in plasma HDL cholesterol and triglycerides with increasing WSDF dose (study 4) is consistent with the findings of the studies reviewed in Table VI. In the current study there were nonsignificant increases in plasma triglyceride concentrations, but these increases were just as large in the groups on placebo as in those on WSDF. It could be that the increases in triglycerides, and the decrease in HDL cholesterol were due to the 15 to 45 g/day of fructose that was used to flavor both the placebo and WSDF mixes.[32]

The NCEP emphasizes that diet and lifestyle modifications are the cornerstone approach to managing elevated blood cholesterol concentrations. These modifications include stopping smoking, regular exercise, losing weight if overweight, and consuming a healthy diet low in saturated fatty acids and cholesterol.[4] Previous studies[5-7,13-24] indicate that diets rich in WSDF can also substantially reduce elevated plasma total and LDL cholesterol concentrations. Unfortunately, recent estimates place the average daily intake of dietary fiber for adult Americans at approximately 7 to 14 g, depending on age, gender and race.[33] In addition, it appears that ≤25% of the total daily dietary fiber intake is obtained from WSDF-rich sources, suggesting that Americans are not fully using the potential cholesterol-lowering benefits of a diet rich in WSDF.[30]

An unexpected finding of the research reported here is that not all WSDF sources appear to lower cholesterol. Studies 1 and 2, which used WSDF from acacia gum as a major source and then as the only source of WSDF, demonstrated no affect on plasma cholesterol concentrations. However, studies 3 and 4 demonstrated that a mixture of WSDF sources (psyllium husk, pectin, and guar and locust bean gums) can be practically incorporated into the diet and result in significant cholesterol-lowering within 4 weeks. It appears appropriate to encourage men and women with elevated cholesterol levels to increase the WSDF in their diet as part of a comprehensive cholesterol management plan.

Additional research is needed to understand the cholesterol-lowering mechanisms and efficacy of the various types of dietary fibers. Also, long-term studies are needed to establish the potential public health benefits of lowering plasma cholesterol concentrations by the incorporation of palatable WSDF-rich foods in the diet.

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Role of Diet and Exercise in the Management of Hyperinsulinemia and Associated Atherosclerotic Risk Factors

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Hyperinsulinemia, hypertension, hypertriglyceridemia and obesity are independent risk factors for coronary artery disease and are often found in the same person. This study investigated the effects of an intensive, 3-week, dietary and exercise program on these risk factors. The group was divided into diabetic patients (non-insulin-dependent diabetes mellitus [NIDDM], n = 13), insulin-resistant persons (n = 29) and those with normal insulin, ≤10 μU/ml (n = 30). The normal groups had very small but statistically significant decreases in all of the risk factors. The patients with NIDDM had the greatest decreases. Insulin was reduced from 40 ± 15 to 27 ± 11 μU/ml, blood pressure from 142 ± 9/83 ± 3 to 132 ± 6/71 ± 3 mm Hg, triglycerides from 353 ± 76 to 196 ± 31 mg/dl and body mass index from 31.1 ± 4.0 to 29.7 ± 3.7 kg/m^2. Although there was a significant weight loss for the group with NIDDM, resulting in the decrease in body mass index, 8 of 9 patients who were initially overweight were still overweight at the end of the program, and 5 of the 8 were still obese (body mass index >30 kg/m^2), indicating that normalization of body weight is not a requisite for a reduction or normalization of other risk factors. Insulin was reduced from 18.2 ± 1.8 to 11.6 ± 1.2 μU/ml in the insulin-resistant group, with 17 of the 29 subjects achieving normal fasting insulin (<10 μU/ml). Blood pressure was reduced from 129 ± 4/84 ± 3 to 124 ± 5/78 ± 2 mm Hg, while triglycerides were reduced from 204 ± 17 to 162 ± 15 mg/dl. Body mass index was reduced from 32.6 ± 5.3 to 31.2 ± 5.1 kg/m^2, with only 4 of 24 who were overweight reaching a normal weight.

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Hyperinsulinemia, hypertension, hypertriglyceridemia and obesity are all independent risk factors for coronary artery disease. The clustering of these risk factors in the same subject, however, greatly increases the risk for coronary artery disease. This clustering has been termed "syndrome X"[1] or "the deadly quartet."[2] Insulin resistance, which leads to hyperinsulinemia, is thought to be the key factor, which then precipitates the other problems, especially in genetically susceptible persons.[3] This investigation tests the hypothesis that lifestyle modification including a low-fat, high-complex-carbohydrate diet combined with daily aerobic exercise can be effective for controlling hyperinsulinemia and the related atherosclerotic risk factors.

METHODS

Patients: Seventy-two subjects (40 men, 32 women) participated in a 26-day residential program at the Pritikin Longevity Center in Santa Monica, California. These subjects were all of the 26-day participants in 8 different sessions at the Longevity Center. The mean age of the participants was 57 ± 13 years (range of 21 to 78). The subjects entered the program of their own volition or upon referral by their physician. They all signed a consent form giving permission to use their data for research purposes.

On arrival, the participants were given an orientation and instructions for a 12-hour fast. The following morning, blood samples were obtained with the subjects seated in an upright position. The samples were analyzed for serum cholesterol, triglycerides, glucose, and other standard tests at SmithKline Beecham Laboratories. Serum insulin was determined at the University of California, Los Angeles, by radioimmunoassay with reagents from ICN Biomedicals, Inc. (Horsham, Pennsylvania).

The participants were subdivided according to their pre-program diagnosis and fasting serum glucose and insulin measurements. Group 1 included patients who were diabetic (non-insulin-dependent diabetes mellitus [NIDDM]); they were taking diabetic medication or had a fasting serum glucose ≥140 mg/dl, or both (n = 13). Group 2 included participants who were insulin-resistant; they had a fasting serum insulin ≥10 μU/ml and a fasting serum glucose <140 mg/dl (n = 29). Group 3 included participants who had normal glucose with a fasting serum insulin <10 μU/ml (n = 30). Twenty-seven of the participants had been through the Pritikin Program anywhere from 1 to 11 years earlier and had returned for a refresher course. There were 3 in

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group 1, 9 in group 2 and 15 in group 3. The average length of time the refreshers in group 3 had been following the diet and exercise program at home was 6.6 ± 0.9 years.

The participants underwent a physical exam by a physician to receive approval for a graded exercise treadmill stress test. Before the treadmill test, body weight and height were measured. The participants were then given a standard 12-lead electrocardiogram at rest and a treadmill stress test according to a modified Bruce protocol. Blood pressure at rest was measured before the test using standard auscultation techniques after several minutes of quiet rest in the supine position. The exercise test was terminated at (1) the participant's decision, (2) 2.0 mm ST-segment depression in the electrocardiogram, (3) blood pressure >220 mm Hg systolic or 110 mm Hg diastolic, (4) +2 angina or claudication pain (on a scale of 1 to 4), or (5) because of other established medical criteria.[4]

Based on the treadmill test results, the participants were provided with an appropriate training heart rate and given an individualized walking program. Generally, the program consisted of walking for a minimum of 30 minutes at their training heart rate 4 to 5 times per week, and once or twice a week upwards of 45 minutes below their training heart rate. The training heart rate was defined as 70 to 85% of the achieved maximal heart rate or 10 to 15 beats below the heart rate at which electrocardiographic abnormalities were observed. At the end of each week, the participants were given a new walking program. In addition to the walking program, each participant attended a supervised exercise class 5 days a week. The class consisted of 10 to 20 minutes of stretching and flexibility exercises and 40 to 50 minutes of aerobic exercise (treadmill or exercycle) at training heart rate levels. The participants were seen by a physician at least twice a week to evaluate their progress and regulate their medication. Diabetic medication was discontinued when fasting glucose decreased to <140 mg/dl and antihypertensive drugs were discontinued when pressure decreased to <140/90 mm Hg. Blood samples were obtained after 3 weeks, and the participants were given a final physical evaluation for data after the program.

TABLE I Mean (±SE) Values at the Beginning and End of the Diet and Exercise Program in 72 Patients*

Variable	Before	After	% ↓
Fasting serum insulin (µU/ml)	17 ± 3	12 ± 2	32
Fasting serum glucose (mg/dl)	117 ± 6	102 ± 4	13
Total cholesterol (mg/dl)	228 ± 6	178 ± 5	22
LDL cholesterol (mg/dl)	143 ± 5	110 ± 4	23
HDL cholesterol (mg/dl)	47 ± 2	38 ± 1	20
Triglycerides (mg/dl)	205 ± 18	151 ± 9	26
Body weight (kg)	88 ± 2	84 ± 2	5
Body mass index (kg/m^2)	30 ± 1	29 ± 1	4
Resting systolic pressure (mm Hg)	128 ± 3	121 ± 3	6
Resting diastolic pressure (mm Hg)	80 ± 1	74 ± 1	8

*All decreases were statistically significant, $p < 0.01$.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

During the 26-day program the participants were served and taught to prepare meals that were in accordance with the guidelines of the Pritikin Eating Plan. Of the total calories, <10% were derived from fat (polyunsaturated/saturated = 1.24), 10 to 15% from protein, and 75 to 80% from carbohydrate. Protein was derived from other than animal sources, with the exception of nonfat milk served daily and small amounts of fish or fowl served twice weekly, not >100 g/week. Carbohydrates were supplied in the form of vegetables, fruits, legumes and whole grains. Thirty-five to 40 g of dietary fiber per 1,000 kcal were provided each day. The diet contained <25 mg of cholesterol and 4 g of sodium chloride per day. Alcohol, tobacco and caffeinated beverages were not permitted during the program. Food was provided ad lib. Persons who were interested in weight reduction were instructed to limit complex carbohydrates to 5 servings, fruit to 3 servings and vegetables to 4 to 8 servings to assure a minimal intake of 1,000 kcal/day. Rapid weight loss was discouraged.

To determine the effectiveness of the diet and exercise program, data before and after the program were analyzed for significant differences using Hotelling's T^2, a multivariate test, followed by paired *t* tests for repeated measures (BMDP statistical software: program 3D). Differences between the subgroups were assessed by a 1-way analysis of variance (BMDP statistical software: program 7D). A p value <0.05 was considered significant. Values are expressed as mean ± standard error.

RESULTS

Total group: Table I lists the values for all parameters before and after intervention. The Hotelling's multivariate test showed that the group changes were highly significant ($T^2 = 597$, $p < 0.0001$). The individual parameter analyses showed that all values after intervention were significantly lower than those before ($p \leq 0.01$). In addition to the reduction in serum insulin and related cardiovascular risk factors, medication was completely discontinued in 6 of 11 diabetic patients and in 4 of 10 hypertensive patients.

Subgroups: The Hotelling's multivariate analyses before and after intervention were significant ($p \leq 0.05$) for all 3 subgroups. Values for glucose, insulin and triglycerides before the study were significantly higher in group 1 (the patients with NIDDM), whereas high-density lipoprotein (HDL) cholesterol was significantly lower. The initial systolic blood pressure was significantly different for all 3 groups, whereas the initial diastolic pressure was significantly lower in group 3. Total and low-density lipoprotein (LDL) cholesterol as well as body weight were significantly lower in group 3 at the start of the intervention.

Figure 1 shows the changes in fasting serum insulin. All 3 groups had significant decreases; however, the decreases observed in groups 1 and 2 were significantly greater ($p < 0.01$) than the small decrease observed for group 3. Serum glucose (Table II) was also significantly reduced in all 3 groups, with the reduction in group 1 being significantly greater than the changes observed for groups 2 and 3. In group 1, 11 of the 13 patients

TABLE II Serum Cholesterol and Glucose Changes in Response to the Diet and Exercise Program

	Total Cholesterol		LDL Cholesterol		HDL Cholesterol		Glucose	
Group	Before	After	Before	After	Before	After	Before	After
1	223 ± 17	174 ± 14	154 ± 17	114 ± 14	37 ± 3	32 ± 4	200 ± 17	144 ± 14
2	240 ± 10	189 ± 9	151 ± 7	116 ± 5	43 ± 3	36 ± 3	103 ± 3	96 ± 2
3	214 ± 9	169 ± 5	132 ± 8	104 ± 5	54 ± 3	41 ± 2	95 ± 2	91 ± 1

All values after the program were significantly lower than values before intervention, $p < 0.01$.
Abbreviations as in Table I.

with NIDDM were taking medication (6 insulin; 5 oral agents). At the end, 4 patients were taking insulin and only 1, oral agents.

Table II lists the changes in cholesterol as a result of the program. All 3 groups had significant reductions in total cholesterol that were not significantly different from each other. LDL cholesterol was also significantly reduced in all 3 groups, and again there was no significant difference in the reductions achieved between the 3 groups. All 3 groups had a significant reduction in HDL cholesterol, with the greatest reduction seen in group 3; the reduction in this group was significantly greater than the reductions seen in the other 2 groups. Although triglyceride levels (Figure 2) were decreased in all 3 groups, the reductions were statistically significant only in groups 1 and 2.

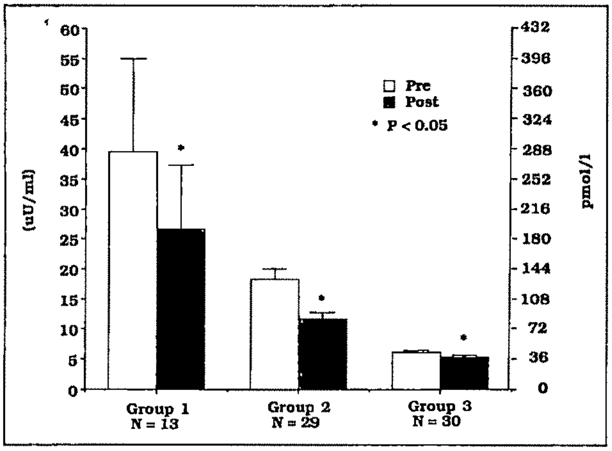

FIGURE 1. Effects of diet and exercise on fasting serum insulin. Group 1 contained patients with non–insulin-dependent diabetes mellitus group 2 insulin-resistant subjects and group 3 subjects with normal insulin (≤10 μU/ml).

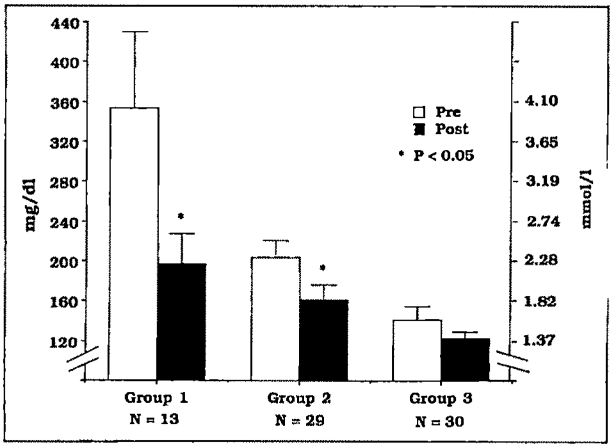

FIGURE 2. The effect of diet and exercise on serum triglycerides.

Body weight decreased significantly in all 3 groups (Table III). The weight loss was not significantly different between the 3 groups. Figure 3 shows the effects of the diet and exercise program on body mass index. According to the definition used by the National Center for Health Statistics for overweight (body mass index ≥27.8 kg/m^2 for men and ≥27.3 kg/m^2 for women), 9 of the 13 patients in group 1, 27 of the 29 patients in group 2, and 12 of the 30 patients in group 3 were overweight. For all 3 groups, body mass index decreased significantly. However, as was the case with body weight, there was no significant difference between the decreases observed for the 3 groups. At the conclusion of the program, 8 of the subjects in group 1, 18 in group 2 and 6 in group 3 were still overweight according to their body mass index.

Systolic blood pressure at rest decreased in all 3 groups; however, the decrease was only significant in group 3 (Table III). On the other hand, diastolic blood pressure at rest decreased significantly in all 3 groups. For both systolic and diastolic blood pressures, the decreases were not significantly different between the 3 groups.

With respect to the medication status of the hypertensive patients, 4 of the 10 diabetic patients (group 1) receiving antihypertensive drugs discontinued medications at the end of the program. Furthermore, 1 of the 10 patients in group 2 and 1 of the 4 patients in group 3 who were receiving antihypertensive medications at the start of the program discontinued medications at discharge.

Although there were significant reductions in all of the risk factors in groups 1 and 2, not everyone was able to completely normalize their risk factors during the 3-week program. However, at the end of the program only 3 of 15 participants still possessed all of the elevated factors that comprise the deadly quartet (Table IV). These data on the refreshers in group 3 fur-

TABLE III Blood Pressure and Body Weight Changes in Response to the Diet and Exercise Program

	Systolic BP (mm Hg)		Diastolic BP (mm Hg)		Body Weight (kg)	
Group	Before	After	Before	After	Before	After
1	143 ± 9	132 ± 6	83 ± 3	71 ± 3	92 ± 4	88 ± 4
2	130 ± 4	125 ± 5	84 ± 3	78 ± 2	99 ± 4	94 ± 3
3	119 ± 3	111 ± 3	75 ± 2	70 ± 2	76 ± 3	73 ± 2

All values after the program were significantly ($p < 0.05$) different from values before, except for systolic blood pressure in groups 1 and 2.
BP = blood pressure.

ther show that there are a few subjects who simply do not respond to this nonpharmacologic intervention and, thus, even with long-term compliance require medication to control certain risk factors.

DISCUSSION

The clustering of atherosclerotic risk factors, hyperinsulinemia, hypertriglyceridemia, hypertension and obesity in the same person has been described by Reaven[1] and Kaplan.[2] In addition to these risk factors it is also now recognized that the same subjects also have depressed HDL cholesterol and elevated blood levels of fibrinogen and plasminogen activator inhibitor, additional risk factors for coronary artery disease.[5-8] More recently DeFronzo and Ferrannini[3] suggested that skeletal muscle insulin resistance leads to hyperinsulinemia, which in turn leads to an elevation of the other risk factors in genetically susceptible persons.

In the present study major reductions in insulin were achieved in both diabetic and insulin-resistant patients, indicating a significant reduction in skeletal muscle insulin resistance. Part of the reduction in serum insulin in diabetic patients was due to a discontinuation of diabetic medication. In a previous study, we reported that skeletal muscle insulin resistance could be induced in rats by placing them on a high-fat, high-sucrose diet similar to the typical U.S. diet.[9] Insulin resistance and down-regulation of insulin receptor tyrosine kinase activity has been found in both obese persons and patients with NIDDM.[10,11] In addition to diet, both acute and chronic exercise can increase insulin sensitivity.[12]

Numerous studies have recently shown a significant correlation between hyperinsulinemia and hypertension as reviewed by Gans and Donker.[13] In the present study blood pressure reductions were achieved in all groups and antihypertensive medications discontinued in several patients. Insulin is thought to influence blood pressure by stimulating sodium reabsorption in the distal tubule, increasing sympathetic nervous system activity to increase peripheral resistance or other mechanisms.[13] These data on blood pressure agree with our earlier data on a much larger group of hypertensive patients ($n = 286$) showing that diet and exercise can be effective, in most cases, for controlling hypertension and eliminating the need for drug therapy.[14] DeFronzo and Ferrannini[3] have pointed out that frequently used antihypertensive drugs (β blockers and thiazide diuretics) impair insulin sensitivity and adversely effect serum lipid profile, indicating that life-style modification would be preferred to several common drug therapies for controlling hypertension.

Elevated serum lipids have long been recognized as important risk factors for coronary artery disease. Although elevated levels of total and LDL cholesterol are not consistently found in hyperinsulinemic patients, compared with typical U.S. levels, elevated triglycerides are one of the features of the deadly quartet.[1-3,6] In the present study all lipid fractions showed significant decreases. The mean reduction in triglycerides in the present study was 26%. These lipid data agree with previously published data from almost 4,600 subjects who attended the Pritikin Longevity Center.[15] The reduction in triglycerides is believed to be due to both diet modification and aerobic exercise. Oscai et al[16] reported that as little as 3 days of a 45-minute walk/jog program reduced elevated triglycerides and normalized serum very low density lipoprotein patterns. The triglyceride level in the 15 refreshers in group 3 was 136 mg/dl on returning to the Center indicating that long-term compliance to a high-carbohydrate diet does not increase triglycerides as some[17-20] have claimed. This is probably due to continued regular exercise and the use of unrefined complex carbohydrates as opposed to carbohydrates with a high glycemic index. Even without exercise, Ullmann et al[21] recently reported that a high-complex-carbohydrate diet did not increase triglycerides if the carbohydrate in the diet was increased gradually.

There is good evidence linking hyperinsulinemia to depressed HDL cholesterol.[1,2,6,7] Thus, it was not surprising to observe in the data before the program that HDL cholesterol was negatively correlated with serum insulin. In response to the intervention, however, HDL cholesterol decreased in all 3 groups. This response is opposite to what might be anticipated with a decrease in insulin. Brinton et al[22] recently conducted HDL–apolipoprotein turnover studies using a similar high-complex-carbohydrate, low-fat diet and found that apolipoprotein A_I, a specific HDL apoprotein, was reduced by 23% because of both a reduction in the rate of synthesis and an increase in the rate of catabolism. They also concluded that it is inappropriate to assume that a low-

TABLE IV Number of Subjects with Elevated Risk Factors* Before and After Intervention

	Insulin	Triglycerides	Blood Pressure	Body Mass Index	Deadly Quartet
Group 1 (n = 13)	10/8	11/6	13/8	9/8	5/1
Group 2 (n = 29)	29/12	16/12	17/10	24/20	10/2
Group 3 (n = 30)	0/0	7/3	6/4	10/6	0/0
Group 3 (refreshers) (n = 15)	0/0	3/3	3/1	3/2	0/0

*Insulin > 10 μU/ml, triglycerides > 150 mg/dl, blood pressure ≥ 140/90 mm Hg or medication, or both, and body mass index ≥ 27.8 or 27.3 kg/m² for men and women.

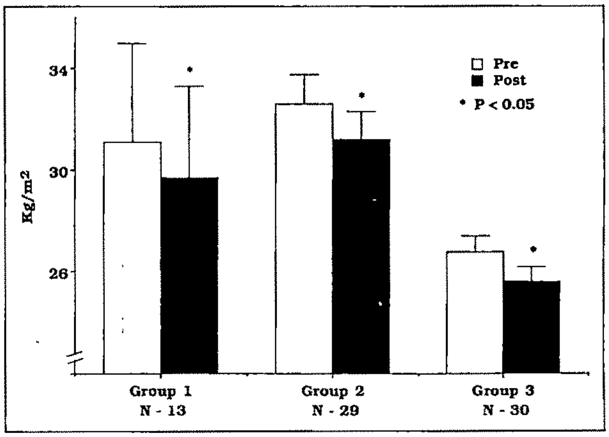

FIGURE 3. Effects of diet and exercise on body mass index.

fat, high-carbohydrate diet-induced decrease in HDL cholesterol carries the same risk of atherosclerosis as does low HDL cholesterol found in persons eating a typical high-fat diet. Whereas low HDL cholesterol has been shown to increase the risk for atherosclerosis in this and other countries with high levels of total and LDL cholesterol, it does not seem to be important in societies with low levels of total and LDL cholesterol due to low-fat diets.[23-27] Recent data from Ornish et al[28] showed that in a 1-year study using a very low-fat, high complex carbohydrate diet, HDL cholesterol was reduced while regression of coronary atherosclerosis was documented, which further demonstrates the lack of significance of a low HDL cholesterol in persons consuming a very low-fat, high-complex-carbohydrate diet.

Obesity, especially obesity of the upper body, has been shown to be an important aspect of insulin resistance and the deadly quartet.[1,2,29] Some workers have suggested that obesity is the cause of the other aspects of the deadly quartet. Although it is true that fasting and postprandial insulin levels have been positively correlated with fat cell size, especially in the upper body fat pads,[29] we have shown in short-term animal studies that hyperinsulinemia can be induced independent of obesity by placing rats on a high-fat, high-sucrose diet.[9] The hyperinsulinemia was shown to result from insulin resistance in skeletal muscle, thus requiring higher insulin levels to normalize serum glucose.

Although pre-program data from the 3 groups would suggest an important role for obesity since group 3 had the lowest body mass index and lowest insulin levels, compared with the other 2 hyperinsulinemic groups, data after the program do not support such a relation. In group 2 (the insulin-resistant group), insulin was significantly reduced as was body mass index; however, on the test after the program, 14 subjects had an insulin level ≤ 10 μU/ml, but only 2 had normalization of body mass index. In fact, 6 subjects still had a body mass index >30 and would be considered obese. The same trend was seen in group 1 (patients with NIDDM). On the post-test, 5 of 13 patients had insulin levels ≤ 10 μU/ml, but only 1 of the 5 had normalization of body mass index. Thus, it appears that obesity itself does not create insulin resistance because many of the subjects in the present study had normalized their insulin levels but were still significantly overweight or obese at the end of the program.

The reductions in insulin observed in the present study may have been due, in part, to a hypocaloric state. This also points out the value of regular exercise combined with a low-fat, complex-carbohydrate diet, not only for reducing insulin but also for helping to normalize body weight. However, data from the refreshers in group 3 indicate that it is not necessary to maintain a hypocaloric state to maintain a low insulin level once an initial weight loss has been achieved. Studies have shown that when humans consume a low-fat, high-complex-carbohydrate diet ad lib they take in fewer calories compared with a high-fat diet like the typical U.S. diet.[30] These data suggest that attention should be focused more on the quality of food consumed as opposed to the quantity of food and weight loss per se.

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ST-Segment Depression During Dipyridamole Infusion, and Its Clinical, Scintigraphic and Hemodynamic Correlates

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Denny D. Watson, PhD, and George A. Beller, MD

The goal of this study was to determine whether dipyridamole-induced ST-segment depression reflects more severe or extensive myocardial hypoperfusion than the absence of this electrocardiographic finding. The clinical, hemodynamic and scintigraphic correlates of ST-segment depression during intravenous dipyridamole infusion were studied in 204 consecutive patients undergoing dipyridamole stress thallium-201 (Tl-201) imaging for evaluation of coronary artery disease. Of 182 patients with a diagnostic baseline electrocardiogram, 28 (15%) developed ST depression after dipyridamole. Patients with ST depression, compared with those without, were older (64 ± 1 vs 60 ± 1 years; $p < 0.03$) and had a higher frequency of chest pain (57 vs 23%; $p < 0.001$) and a higher heart rate-blood pressure product (12.7 ± 0.6 vs $11.2 \pm 0.2 \times 10^3$; $p < 0.008$) after dipyridamole. Patients with ST depression were more likely to have Tl-201 redistribution (64 vs 38%; $p < 0.02$) and a greater number of redistribution defects (2.3 ± 0.04 vs 0.9 ± 0.1, $p < 0.001$) than were those without ST depression.

By multivariate logistic regression analysis, the most powerful correlate of ST depression was the number of segments having Tl-201 redistribution ($p < 0.001$). Other independent correlates were presence of chest pain, heart rate at Tl-201 injection, and age. Thus, the determinants of dipyridamole-induced ST-segment depression include the scintigraphic extent of reversible hypoperfusion, as well as indexes of myocardial oxygen demand.

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Dipyridamole-induced ST-segment depression occurs in differing clinical populations with an incidence of 8 to 40%.[1-3] This electrocardiographic response to pharmacologic stress has been described most often in patients with coronary artery disease (CAD),[3-5] as well as in those with hypertension,[6] Syndrome X[7] and acute rejection after cardiac transplantation.[8] In patients with known CAD, dipyridamole thallium-201 (Tl-201) scintigraphy provides information concerning the functional severity of disease (e.g., extent of perfusion abnormalities). In some cases, dipyridamole-induced Tl-201 defects may indicate true ischemia, resulting in symptoms or electrocardiographic changes, or both, rather than just reflecting heterogeneity of flow reserve.[9] Although angiographic correlates of ST-segment depression occurring with dipyridamole infusion have been described,[5] it has not been clearly ascertained whether this ST depression reflects more severe or extensive hypoperfusion, or the associated hemodynamic changes induced by the drug. This study examines the hemodynamic and Tl-201 scintigraphic correlates of dipyridamole-induced ST-segment depression.

METHODS

Patient population: The study population consisted of 204 consecutive patients who were referred between June 1988 and October 1990 to the University of Virginia Health Sciences Center for dipyridamole stress Tl-201 testing for the evaluation of CAD. The usual exclusion criteria for dipyridamole testing were used, including age <75 years, unstable angina pectoris, underlying bronchospastic disease and chronic aminophylline use. No changes were made in patients' prescribed drug regimens before the test, except that those receiving theophylline-containing drugs were not included in the study unless such drugs were discontinued ≥72 hours earlier.

A nondiagnostic electrocardiogram was defined as a baseline tracing demonstrating underlying left bundle branch block, a paced rhythm or significant (>0.5 mm) resting ST-segment depression, as with left ventricular hypertrophy or digitalis effect.[10] Twenty-two patients (11%) were excluded from the analysis owing to the presence of any 1 of these findings. The remaining 182 patients (104 men and 78 women, mean age 61 ± 10 years) constituted the study population.

Imaging protocol: The dipyridamole Tl-201 imaging protocol used at our institution has been previously described.[11] With patients in the supine position, dipyridamole was administered intravenously at a dose of 0.56

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TABLE I Univariate Clinical and Hemodynamic Correlates of Dipyridamole-Induced ST-Segment Depression

Variable	ST Depression (n = 28)	No ST Depression (n = 154)	p Value
Clinical			
Age (yr)	64 ± 1	60 ± 1	<0.03*
Men/women	13/15	91/63	0.22
Chest pain	16 (57%)	35 (23%)	<0.001*
β-blocker use	6 (21%)	37 (24%)	0.99
Hemodynamic			
Systolic blood pressure (mm Hg)			
Baseline (before dipyridamole)	156 ± 5	145 ± 2	<0.02*
Tl-201 injection	144 ± 4	137 ± 2	0.17
Heart rate (beats/min)			
Baseline (before dipyridamole)	73 ± 2	71 ± 1	0.49
Tl-201 injection	88 ± 2	82 ± 1	<0.03*
Rate-pressure product (× 10^3)			
Baseline (before dipyridamole)	11.5 ± 0.5	10.3 ± 0.2	<0.03*
Tl-201 injection	12.7 ± 0.6	11.2 ± 0.2	<0.008*
Change after dipyridamole			
Systolic blood pressure (mm Hg)	−12 ± 4	−7.3 ± 1	0.12
Heart rate (beats/min)	15 ± 2	10 ± 1	<0.03*
Rate-pressure product (× 10^3)	1.3 ± 0.5	0.9 ± 0.2	0.4

*Statistically significant difference.
Tl-201 = thallium-201.

mg/kg over the course of 4 minutes, followed by the injection of 2.0 mCi of Tl-201, 3 minutes thereafter. Blood pressure, heart rate and a 12-lead electrocardiogram were obtained at baseline and every minute for the first 10 minutes, every 2 minutes for the next 10 minutes, and every 5 minutes for the remaining 25 minutes of monitoring. Anterior and 45° and 70° left anterior oblique planar images were obtained 10 minutes and 2.5 hours after Tl-201 administration.

Electrocardiographic analysis: ST-segment motion was analyzed in each of the serially obtained 12-lead electrocardiograms by 1 investigator. The interpreter had no knowledge of patient identity or scintigraphic results. As with standard exercise stress testing,[12] dipyridamole-induced ischemia was defined as the occurrence of ≥ 1 mm horizontal or downsloping ST-segment depression during or after dipyridamole infusion.

Quantitative image analysis: Quantitative image analysis was performed using a computer-assisted method previously described by our laboratory.[13] Using an 11-segment model,[14] background-subtracted Tl-201 images were analyzed by 2 observers with respect to presence or absence of initial defects and subsequent redistribution, using previously established criteria.[13] Abnormal scans were assessed as demonstrating either a 1- or multivessel CAD pattern, according to conventional definitions.[15] A third observer resolved differences in interpretation. Image analysis was performed without knowledge of the patient's electrocardiographic findings.

Lung Tl-201 uptake was measured over the midleft lung field in the anterior view. The lung/heart ratio was expressed as the ratio of counts in this lung region to peak myocardial counts.[14] Abnormal lung Tl-201 uptake was defined as a peak lung/heart ratio >0.51.[14]

The Tl-201 imaging variables documented in this study included presence of redistribution, left ventricular dilatation, abnormal lung Tl-201 uptake and multivessel CAD pattern. The numbers of redistribution and persistent defects were recorded for each patient. Partial redistribution was considered in the general redistribution category.

Statistical analysis: Data were expressed as mean ± SEM or as proportions. For univariate analysis, differences between mean values were determined using 2-tailed *t* tests; Fisher's exact test was used to assess differences in proportions.

Stepwise multiple logistic regression analysis was used to determine which of the significant univariate correlates of ST-segment depression remained independently significant on multivariate analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Univariate analysis: CLINICAL AND HEMODYNAMIC VARIABLES: Of 182 patients with a diagnostic baseline electrocardiogram, 28 (15%) developed ST-segment depression during or after dipyridamole infusion. Table I lists the significant univariate clinical and hemodynamic correlates of dipyridamole-induced ST depression. Patients with ST depression, compared with those without, were older (64 ± 1 vs 60 ± 1 year; $p < 0.03$) and more likely to experience chest pain (57 vs 23%; $p < 0.001$). There was no difference between the 2 groups with respect to gender or use of β-blockers.

The rate-pressure product before dipyridamole was higher in patients developing than those without ST depression, probably due to a higher baseline systolic blood pressure in the ST-depression group (Table I). After dipyridamole infusion, the rate-pressure product was even higher in the ST-depression than the normal group ($p < 0.02$) due to a greater increase in heart rate in those with ST depression.

THALLIUM-201 SCINTIGRAPHIC VARIABLES: The scintigraphic correlates of ST depression are illustrated in Figure 1. Patients with dipyridamole-induced ST depression were more likely to develop Tl-201 redistribution than those with normal electrocardiographic responses (64 vs 38%; $p < 0.02$) (Figure 1A). Similarly, the ST-depression group had a significantly greater number of myocardial segments exhibiting Tl-201 redistribution than the group without ST depression (2.3 ± 0.4 vs 0.9 ± 0.1; $p < 0.0001$) (Figure 1B). A multivessel CAD pattern, defined as defects in the distribution of >1 of the 3 major coronary supply regions (e.g., left anterior descending and right coronary arteries), was more frequently seen in patients with than without ST depression (32 vs 16%; $p < 0.05$). Although left ventricular cavity dilatation tended to occur more frequently in those with than without ST depression (18 vs 10%), this difference did not achieve statistical significance. There was no significant difference between the 2 groups with respect to incidence of abnormally increased Tl-201 lung uptake or number of fixed defects.

Multivariate analysis: The univariate correlates of dipyridamole-induced ST depression were entered into a stepwise logistic regression model. The most powerful correlate of ST depression in this model was the number of myocardial segments demonstrating Tl-201 redistribution ($\chi^2 = 16.84$; $p < 0.001$). Other independent correlates of dipyridamole-induced ST-segment depression on multivariate analysis were the occurrence of chest pain ($\chi^2 = 14.53$; $p < 0.001$), heart rate at time of Tl-201 injection ($\chi^2 = 5.78$; $p < 0.02$), and patient age ($\chi^2 = 4.67$; $p < 0.04$).

DISCUSSION

The major finding of this study was that ST-segment depression in response to dipyridamole was most strongly correlated with the extent of reversible myocardial hypoperfusion (i.e., it correlated with the extent of myocardium rendered hypoperfused by quantitative scintigraphic criteria). In this series of consecutive patients referred for dipyridamole Tl-201 stress testing for standard indications, we found that 15% developed ST-segment depression in response to infusion of the drug, an incidence similar to that described by other investigators.[1-5]

By univariate analysis, patients with ST depression were older and more likely to experience chest pain. These patients had a higher baseline rate-pressure product and a greater increase in heart rate in response to dipyridamole, suggesting that increased oxygen demand may also contribute to the development of ST depression after dipyridamole.

Significant univariate Tl-201 scintigraphic correlates of ST depression were the number of redistribution defects per patient, and therefore, not surprisingly, presence of a multivessel CAD pattern.

The most powerful independent correlate of dipyridamole-induced ST-segment depression on multivariate analysis was the number of segments showing redistribution. Because the number of redistribution defects most strongly correlates with ST depression, the extent of reversible hypoperfusion in response to pharmacologic stress may be the major determinant of this abnormal electrocardiographic response.

Since ST depression with stress is indicative of true ischemia,[16] it is likely that patients exhibiting this response have a mismatch between regional flow (oxygen supply) and oxygen demand. This could occur with flow decreasing to below baseline levels, particularly in the endocardium.[17,18] Coronary "steal," where subendocardial flow is reduced to abnormal levels in the supply region of a stenotic coronary artery, is a well-described phenomenon seen with dipyridamole or adenosine infusion in the experimental laboratory.[17,19] Alternatively or additionally, oxygen supply-demand mismatch could occur with a significant increase in heart rate consequent to dipyridamole infusion. Perhaps, as suggested by the findings of this study, both mechanisms are important for producing ST depression.

Comparison with previous studies: Although several other studies characterized the correlates of dipyridamole-induced ST depression,[5,20-22] this is the first study documenting that dipyridamole-induced ST depression is associated with the scintigraphic extent of jeopardized myocardium. Unlike other published reports, this study involved an unselected, consecutive group of patients referred for dipyridamole stress testing.

Chambers and Brown,[5] in a smaller population of patients undergoing dipyridamole Tl-201 testing in addition to cardiac catheterization, found that the presence of "good" coronary collaterals was most strongly associated with ST depression on multivariate analysis, even amongst the subgroup with the most severe CAD. Presence of redistribution was a significant correlate of ST depression by univariate analysis only. In that study, quantitation of the number of redistribution defects was not reported. Multivessel disease documented by cardiac catheterization tended to be more frequent in patients with than without ST depression (71 vs 56%), which is consistent with our own scintigraphic results. As with our study, Leppo et al[4] found an association between ST depression and indexes of myocardial oxygen demand.

In an analysis of 30 patients undergoing dipyridamole Tl-201 imaging and cardiac catheterization, Laarman et al[3] found that ST depression correlated with presence of CAD, but they did not report a relation with the extent of CAD.

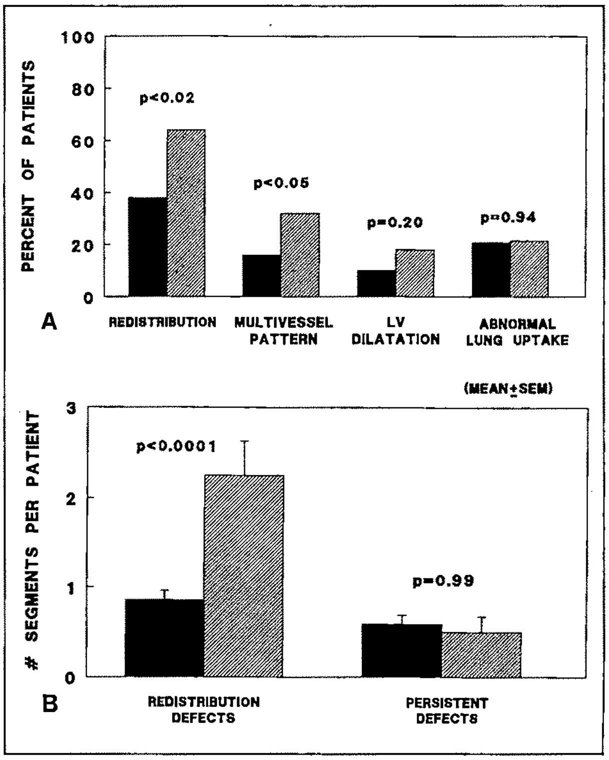

FIGURE 1. Scintigraphic correlates of dipyridamole-induced ST-segment depression. *A*, percentage of patients with particular scintigraphic finding. *B*, number of scan segments per patient. *Solid bar* represents patients without ST depression. *Hatched bar* represents patients with ST depression. LV = left ventricular.

As in the present study, Zhu et al[22] and Pearlman and Boucher[23] found an association between the occurrence of chest pain and dipyridamole-induced ST-segment depression. Other nonscintigraphic studies compared ST depression during exercise testing with that during dipyridamole infusion using body-surface mapping and found concordant results between the 2 methods of stress electrocardiographic testing.[24,25]

Study limitations: This study comprised patients consecutively referred for dipyridamole Tl-201 testing, most of whom did not undergo cardiac catheterization. Thus, parallel angiographic data were not available for our analysis. However, our data do suggest that ST depression reflects more severe CAD than does absence of ST depression.

Additionally, an ultimate use of ST-segment analysis during dipyridamole Tl-201 testing could be its additive value to the patient's risk assessment. Because ST depression correlates with the extent of myocardium at risk, it could have prognostic value. Whereas some studies involving select populations assigned prognostic value to this finding,[25] others did not.[2,27] Because we did not have systematic follow-up on the patients included in our study, we cannot ascertain if ST-segment depression would have similar prognostic value in a more general population referred for dipyridamole testing. This would be a subject for more comprehensive prospective analysis.

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Effect of Dipyridamole Therapy on Myocardial Ischemia in Patients with Stable Angina Pectoris Receiving Concurrent Anti-ischemic Therapy

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The effects of oral dipyridamole on exercise performance and anginal symptoms were evaluated in 15 men with stable angina pectoris. In a double-blind, randomized, crossover design, patients received 75 mg of dipyridamole or placebo every 8 hours for 2 weeks in addition to their previously prescribed cardiac medications. Graded exercise tolerance testing was performed twice before randomization, at the end of each treatment period, and after single-blind placebo washout. When compared with baseline tests, the time to onset of 0.1 mV ST-segment depression was similar between dipyridamole and placebo treatments (316 ± 89 vs 345 ± 102 seconds, respectively, p = not significant). No significant differences existed between treatments in the peak systolic blood pressure–heart rate product or in the duration of exercise. Angina pectoris occurred during all 3 baseline exercise tests in 7 of the 15 subjects; the time to onset of angina was unchanged by either treatment.

Analysis of symptom diaries conducted in 13 patients revealed no significant alteration in reported anginal symptoms during dipyridamole treatment compared with placebo treatment (0.6 ± 0.9 vs 0.3 ± 0.4 episodes per week). Ambulatory electrocardiographic monitoring in 12 patients revealed few episodes of ischemia during daily activities with no alteration in frequency of episodes during treatment periods. Plasma concentrations of dipyridamole did not correspond with the outcomes of exercise testing. It is concluded that chronic oral dipyridamole therapy given in its usual clinical dose does not adversely affect exercise performance, daily anginal episodes or ambulatory ischemia in patients receiving concurrent anti-ischemic medication.

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Dipyridamole is a pyrimidopyrimidine compound that is frequently prescribed as an antiplatelet agent in thromboembolic disorders.[1,2] It also is known to increase coronary blood flow primarily through the dilation of the smaller resistance arteries.[3] In the presence of coronary artery disease, the drug creates a redistribution of blood flow away from myocardium distal to the occluded vessels. As a result, large doses of dipyridamole have been used clinically to produce reversible thallium-201 defects in patients unable to exercise.[4–7] In approximately 8 to 20% of these subjects, the drug causes clinically evident myocardial ischemia.[8]

Although this technique is useful for the diagnosis of coronary artery disease, it highlights the potential for worsening myocardial ischemia in patients given dipyridamole for other purposes. Myocardial ischemia has been reported in patients receiving doses of 75 to 100 mg of dipyridamole before urgent coronary revascularization procedures.[9,10] The purpose of the present study was to determine the effects of chronic oral dipyridamole therapy on clinical and exercise-induced myocardial ischemia in patients with chronic stable angina pectoris receiving concomitant anti-ischemic medications.

METHODS

Patient selection: Clinically stable patients aged 52 to 70 years with ischemic coronary artery disease were identified through the results of exercise thallium-201 myocardial scintigraphy performed at The Memorial Hospital of Rhode Island. Study entry criteria included exercise-induced electrocardiographic changes of ≥0.1 mV horizontal or downsloping ST-segment depression, total exercise duration ≥3 minutes, and a reversible thallium-201 defect. All patients had a history of stable angina pectoris. Further documentation of ischemic heart disease was confirmed by cardiac catheterization or history of myocardial infarction, or both, in some patients.

Patients with electrocardiographic criteria for left ventricular hypertrophy, bundle branch block, baseline ST-segment abnormalities or medication use, such as digoxin making the exercise electrocardiogram uninterpretable, were excluded. Patients receiving dipyridamole, aspirin, nonsteroidal antiinflammatory agents or methylxanthines were also excluded from participation unless the medications could be successfully discontinued for ≥2 weeks before entry into the study.

Experimental design: This was a double-blind, randomized, crossover trial with 2 treatment periods sepa-

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rated by a single-blind placebo washout phase. The study design is depicted in Figure 1. The effects of dipyridamole on myocardial ischemia were assessed using repeated exercise testing, ambulatory electrocardiographic monitoring and the incidence of angina pectoris and nitroglycerin use during the study periods.

After medical screening, patients were randomly assigned to receive 75 mg of dipyridamole (Persantine® 25 mg ×3 in gelatin capsules) or lactose placebo, every 8 hours for 14 days. After a 1-week single-blind placebo washout, patients were crossed over to receive the second study medication every 8 hours for 14 days. Sublingual nitroglycerin, 0.4 mg, was given to each patient to be taken on an as-needed basis during the study. Patients continued to receive their prescribed anti-ischemic drug regimens, which remained unchanged throughout the entire study period.

Exercise testing: Five symptom-limited exercise tests using the Bruce Protocol were performed: twice at baseline, at the end of each treatment period, and after the single-blind placebo washout. If by open analysis the baseline exercise tests were substantially different (i.e., $\geq$1.5 minutes) with regard to time to significant ST segment change, a third baseline test was administered 1 week later with the results of the last 2 tests averaged. Similarly, if the washout exercise test was significantly different from the mean of the 2 baseline tests by open evaluation, single-blind placebo was continued for 1 more week and a repeat exercise test was performed. The second of these 2 tests was then used for comparison. By study protocol, 1 patient performed 3 baseline exercise tests and another completed 2 exercise tests after the single-blind placebo phase.

All tests were administered on a Marquette Series 1800 treadmill using a Delmar Avionics Cardioguard 4000 electrocardiographic recorder; standard test termination criteria, as defined by Ellestad,[11] were used. Evaluation points included time to onset of 0.1 mV horizontal or downsloping ST-segment depression, time to onset of angina pectoris, and total exercise duration. The heart rate–systolic blood pressure product was calculated at each of these events. After completion of the study, the results of all exercise tests were analyzed by 2 of the investigators unaware of the identity of the patient and the treatments at the time of the test.

Ambulatory electrocardiographic monitoring: Three-channel ambulatory electrocardiographic monitoring and analysis using a Marquette model 2 system with a model 8500 recorder were performed in patients during the initial 48 hours of the baseline period and during the last 48 hours of each treatment period. Results were interpreted by a cardiologist not associated with the study and by 2 of the investigators unaware of the patients' clinical characteristics. An ischemic event on the ambulatory electrocardiogram was defined as ST-segment depression of $\geq$0.1 mV with a duration $\geq$1 minute.[12] The ambulatory electrocardiogram was evaluated for the number, duration and magnitude of each ST-segment depression during the recording period. The total amount of significant ST-segment change during the entire monitoring period was summated and standardized per 24 hours for each patient.

Clinical event assessment: Anginal diaries were given to patients at the start of the study, and were reviewed with the patient at each subsequent laboratory visit. Evaluations included the self-reported number of anginal episodes and the quantity of sublingual nitroglycerin tablets used. Patients were also questioned at each visit as to the occurrence of any untoward effects from the study medications.

Biochemical procedures: Resting blood samples for dipyridamole concentrations were obtained immediately before exercise testing at the end of both double-blind treatment periods. Patients were in a fasting state and had ingested the last dose of study medication 2 hours before sampling. Fresh blood (0.9 ml) was collected with 0.1 ml of the anticoagulant trisodium citrate 3.8% and the cell-free plasma was prepared by centrifugation (12,000 g for 3 minutes). Dipyridamole extraction and high-performance liquid chromatographic measurements were performed as described.[13]

Statistical analysis: Statistical analyses of exercise and ambulatory electrocardiographic data were completed with repeated-measures analysis of variance[14,15] using the Biomedical Statistical Package Program 2V.[16] The results of the 3 baseline exercise tests were averaged for the analyses and then compared with placebo and dipyridamole treatments. The incidence of anginal symptoms and nitroglycerin use were analyzed by the Friedman 1-way analysis of variance.[17] The relationships between plasma dipyridamole and the exercise test results were analyzed by a Pearson product moment correlation.[18] The statistical significance level was set at $p \leq 0.05$. The data are reported as the mean value ± standard deviation.

RESULTS

Sixteen men with a history of angina pectoris were randomized to drug treatment and completed the study. One patient was retrospectively excluded from analysis because of an equivocal electrocardiogram, leaving 15 patients for evaluation. The mean age of the subjects was 63 ± 5 years. Four patients had a history of prior myocardial infarction, whereas 3 subjects had previous-

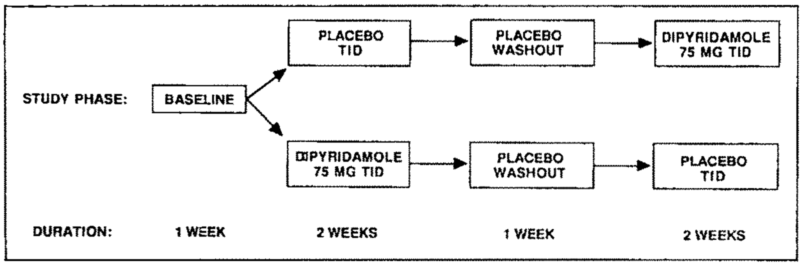

FIGURE 1. Flow diagram of the 6-week double-blind crossover protocol.

TABLE I Effects of Chronic Dipyridamole Therapy on Exercise Tolerance Testing in 15 Patients

	Baseline	Dipyridamole	Placebo	p Value*
Time to 0.1 mV ST-segment depression (s)	324 ± 93	316 ± 89	345 ± 102	NS
HR × BP at significant ST-segment change (× 10^3)	15.6 ± 2.3	15.4 ± 3.1	15.4 ± 2.9	NS
HR at ST-segment change	102 ± 14	99 ± 15	103 ± 15	NS
Duration of ETT (s)	540 ± 105	557 ± 129	532 ± 105	NS
HR × BP at peak exercise (× 10^3)	20.2 ± 3.7	20.2 ± 4.3	19.3 ± 4.3	NS
HR at peak exercise	120 ± 18	121 ± 20	117 ± 20	NS
Time to angina pectoris (s) (n = 7)	419 ± 100	456 ± 159	415 ± 150	NS
HR × BP at angina pectoris (× 10^3) (n = 7)	18.4 ± 3.0	18.5 ± 3.8	19.6 ± 3.3	NS
HR at angina pectoris	113 ± 15	116 ± 16	116 ± 15	NS

*Comparison between baseline, dipyridamole and placebo.
BP = blood pressure; ETT = exercise tolerance testing; HR = heart rate; HR × BP = heart rate–systolic blood pressure product; NS = not significant.

TABLE II Effects of Chronic Oral Dipyridamole Therapy on Ambulatory Electrocardiographic Monitoring in Eight Patients

	Baseline	Dipyridamole	Placebo	p Value*
Duration of monitoring (hours)	43 ± 11	38 ± 13	43 ± 9	NS
No. of episodes of ST-segment depression per 24 hours	1.2 ± 1.8	2.3 ± 3.2	2.0 ± 3.5	NS
Mean amount of ST segment depression per 24 hours (min)	3.5 ± 4.6	15.6 ± 21.1	8.2 ± 13.0	NS
Maximal degree of ST-segment depression (mV)	0.25 ± 0.10	0.25 ± 0.13	0.18 ± 0.05	NS

*Comparison between baseline, dipyridamole and placebo.
NS = not significant.

ly undergone coronary artery bypass graft surgery. Each patient was receiving at least 1 anti-ischemic medication, with 33% receiving combination therapy. Overall compliance with the study medication was 98 ± 4% with no difference between the dipyridamole and placebo treatment periods (97 ± 5 and 99 ± 3%, respectively). One patient received 2 extra weeks of single-blind placebo and 1 patient received an extra week of double-blind placebo due to scheduling difficulties.

The effects of dipyridamole on exercise testing parameters in the 15 patients are listed in Table I. When compared with baseline, the time to onset of ST-segment depression and exercise duration were similar with either placebo or dipyridamole therapy. The heart rate–systolic blood pressure product at the onset of ischemia and at peak exercise was also unaltered. Seven of the 15 patients had reproducible angina pectoris during each of the 3 baseline exercise tests. In these patients, the time to the onset of angina pectoris remained the same after long-term therapy with either dipyridamole or placebo. The heart rate–systolic blood pressure product at the onset of angina pectoris was unchanged by treatment with dipyridamole.

Ambulatory electrocardiographic monitoring data were evaluable in 11 of the 15 patients. Overall, there were no significant differences between baseline and either of the 2 treatment phases. Three of the 11 patients had no significant ST-segment change during any of the monitoring periods. The remaining 8 patients were evaluated separately (Table II). There were no statistical differences between dipyridamole and placebo treatments when compared with baseline in the 8 patients.

Thirteen of the 15 study patients had evaluable anginal diaries. There was a low incidence of symptoms throughout the study and there were no significant differences in anginal episodes per week between baseline, placebo and dipyridamole periods (0.4 ± 0.5, 0.3 ± 0.4 and 0.6 ± 0.9, respectively). The number of sublingual nitroglycerin tablets required per week was low in the study group at baseline (0.08 ± 0.28) and was unaltered by placebo and dipyridamole treatments (0.04 ± 0.14 and 0.27 ± 0.73, respectively).

Blood concentrations of dipyridamole obtained in 12 patients ranged from 2.4 to 18.2 μM (mean 6.6 ± 4.4 μM). Samples from the remaining 3 patients could not be evaluated. There was no significant relationship between the dipyridamole concentration and the change from baseline of any of the exercise test parameters: time to onset of angina ($r = 0.52$) or 0.1 mV ST-segment depression ($r = 0.29$) or exercise duration ($r = 0.08$).

Adverse effects possibly related to study medication were reported in 6 patients during dipyridamole ingestion and 2 during the placebo treatment phase. The most common complaint with dipyridamole was headache (3 patients). One episode each of fatigue, feeling cold and loose stools were reported during dipyridamole treatment, whereas 1 episode of fatigue and 1 of diarrhea were reported during the placebo phase.

DISCUSSION

The chronic use of dipyridamole in the United States is widespread. In 1990, Persantine was the fifty-seventh most frequently refilled prescription, with 3 generic formulations also in the top 200.[2] Since the agent is used primarily for its antiplatelet properties, it is likely that many patients receiving the drug have cardiovascular disease. In light of its ability to produce myocardial ischemia at high doses for pharmacologic stress testing[8] and at lower doses in patients with unstable coronary artery disease,[9] knowledge of the impact of clinical dosages of dipyridamole on patients with chronic myocardial ischemia is clearly important.

The present study evaluated the effects of chronic oral dipyridamole therapy on myocardial ischemia using exercise testing, 48-hour electrocardiographic monitoring and anginal diaries. The results showed no proischemic effects of dipyridamole in clinically stable patients with ischemic coronary artery disease taking concomitant antianginal medications.

The results of the present trial would appear to be in conflict with those of a recently published study by Tsuya et al.[19] These investigators of a double-blind crossover study concluded that 150 mg/day of dipyridamole produced improvement in some patients, whereas others had no alteration or aggravation of exercise-induced myocardial ischemia when compared with placebo. Unlike the present study, 50% of the subjects tested by Tsuya had had recent coronary events and this may account for the varied outcomes of the study.

However, an alternative explanation may be found in the statistical interpretation of the data by Tsuya et al. Using paired *t* test comparisons of the data, there was no significant difference between the duration of exercise after dipyridamole and placebo treatments (323 ± 138 and 313 ± 110 seconds, $p > 0.05$). In addition, time to onset of 0.1 mV ST-segment depression was similar between dipyridamole and placebo (167 ± 66 and 170 ± 68 seconds, $p > 0.05$). Thus, on group analysis, the data of Tsuya et al support the findings of the present study.

In the present trial, 225 mg of dipyridamole per day was given. This is the standard dose given to patients for its antiplatelet purposes. After 2 weeks of treatment, measured concentrations of dipyridamole varied substantially from 2.4 to 18.2 μM. This variability in plasma concentration is expected since the bioavailability of dipyridamole can range from 27 to 66%.[1] However, the mean level of 6.5 μM was similar to that reported when a suspension of 300 mg of crushed dipyridamole was given as a pharmacologic stress agent.[20] Because perfusion defects and ischemia are produced by high-dose oral dipyridamole (300 to 400 mg), an assumption might be made that the similar blood levels found in the current study would produce a detrimental increase in ischemia by dipyridamole. This is not borne out by the results of the trial.

The intent of this study was to investigate the impact of dipyridamole in the usual clinical setting of patients with coronary artery disease, i.e., in the presence of anti-ischemic medication. As such, it was not possible to determine the effect of dipyridamole and its variable concentrations when used as a sole agent in this patient population. In conclusion, dipyridamole given in the clinical dose of 75 mg 3 times daily is not proischemic in patients with stable coronary artery disease when used in conjunction with anti-ischemic medications.

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Plasma Platelet-Derived Growth Factor Levels in Coronary Circulation in Unstable Angina Pectoris

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To examine whether plasma platelet-derived growth factor (PDGF) levels are elevated in the coronary circulation of patients with unstable angina, the plasma PDGF levels in the coronary sinus and aortic root were simultaneously examined in 14 patients with unstable angina, 15 with stable exertional angina, and 15 control subjects. The mean plasma PDGF level (pg/ml) in the coronary sinus was significantly higher ($p < 0.01$) in patients with unstable angina than in those with stable exertional angina and in control subjects (502.1 ± 98.7 vs 301.3 ± 62.5, and 312.7 ± 62.6). However, there were no significant differences in mean plasma PDGF levels in the aortic root among the 3 groups. It is concluded that PDGF release is increased in the coronary circulation in patients with unstable angina.

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The mechanism of unstable angina is thought to be progression of atherosclerosis, thrombosis, coronary spasm and platelet aggregation.[1] Platelet-derived growth factor (PDGF) is now recognized as a ubiquitous growth factor that can be synthesized and secreted by a number of different cell types, including platelets, appropriately activated macrophages and endothelial cells, and numerous transformed cells.[2] PDGF may induce smooth muscle proliferation and accelerate atherosclerosis.[3] PDGF was also found to be a potent vasoconstrictor.[4] Therefore, PDGF may play an important role in the pathogenesis of unstable angina. However, there have been no reports on plasma PDGF levels in patients with unstable angina. The purpose of this study was to determine whether plasma PDGF levels are elevated in the coronary circulation in patients with unstable angina by using a radioimmunoassay. Therefore, we examined the plasma PDGF levels in the coronary sinus and aortic root simultaneously in unstable angina, stable exertional angina and control patients.

METHODS

Patients: We studied 43 patients who underwent diagnostic catheterization. These patients were divided into 3 groups: unstable angina, stable exertional angina and control. The unstable angina group consisted of 14 patients (10 men and 4 women, age range 51 to 76 years [mean 65]). Unstable angina was defined as worsening effort or rest angina, or both, within 1 month of catheterization, with no evidence of myocardial necrosis by enzymatic techniques. The stable exertional angina group consisted of 15 patients (10 men and 5 women, age range 51 to 74 years [mean 64]). All patients with stable exertional angina had typical exertional angina documented by treadmill exercise test with evidence of ischemic ST-segment depression. The control group consisted of 15 patients (10 men and 5 women, age range 51 to 72 years [mean 62]). All patients in the control group had atypical chest pain and were negative for ischemia on treadmill exercise test. The 3 groups were matched for age, gender, diabetes mellitus, hypertension and history of smoking. The unstable and stable exertional angina groups were matched for medications such as long-acting nitrates, calcium antagonists and β blockers. Only 1 patient in the stable exertional angina group was receiving insulin. No patient received coumarin anticoagulants or antiplatelet agents. Patients with previous myocardial infarction, intermittent claudication or other clinical evidence of peripheral vascular or cerebrovascular disease, renal disease, inflammatory connective tissue disease and coronary bypass surgery performed before the study were excluded. The clinical characteristics of the 3 groups are listed in Table I.

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TABLE I Characteristics of the Study Groups

	Unstable Angina	Stable Exertional Angina	Control
No. of Pts.	14	15	15
Age (yr)			
Mean ± SD	65.1 ± 10.0	63.9 ± 5.1	61.9 ± 8.2
Range	51–76	51–74	51–72
Men/women	10/4	10/5	10/5
Diabetes mellitus (n)	3	4	2
Blood pressure > 150/90 mm Hg (n)	6	6	7
Smoking history (n)	8	8	7
Medication used (n)			
Long-acting nitrates	11	9	0
Calcium antagonists	12	10	6
β blockers	1	2	1

Written informed consent was obtained from each patient, and the study was performed in accordance with guidelines approved by the Kumamoto University Medical School ethics committee.

Procedures for catheterization and blood sampling: Conventional, 6Fr Goodale-Lubin and 8Fr Sones catheters (USCI, Billerica, Massachusetts) were used in this study. A woven dacron 6Fr Goodale-Lubin catheter for coronary sinus blood sampling was inserted through the right antecubital vein and was advanced into the coronary sinus. The position of the coronary sinus catheter was confirmed by injecting a small amount of contrast medium. Immediately after this procedure, coronary arteriography was performed by Sones technique, using a woven dacron 8Fr Sones catheter through which blood samples from the aortic root were obtained. All patients received 5,000 U of heparin at the insertion of the Sones catheter. After control left and right coronary angiography, blood samples were collected from the coronary sinus and aortic root simultaneously at the same speed. The time interval from catheter insertion to blood samplings was 15 minutes in all 3 groups. After the initial 3 ml of blood were discarded, 4.5 ml of blood were collected in a sequential manner directly into syringes and were mixed with a 0.5 ml mixture of 15 mmol/liter of theophylline, 3.7 mmol/liter of adenosine, 0.198 mmol/liter of dipyridamole, and 0.11 mol/liter of sodium citrate. The blood samples that were not obtained smoothly were judged to be inappropriate and were discarded. The mixtures of samples and theophylline, adenosine, dipyridamole and sodium citrate were centrifuged ≥15 minutes later, but <30 minutes, at 3,000 rpm at 4°C for 30 minutes. Plasma was separated immediately and fast frozen at −20°C for ≤24 hours and subsequently at −80°C before assay. The assay was performed within 1 month.

Radioimmunoassay of platelet-derived growth factor: CHEMICALS: Recombinant PDGFc-sis and Bolton-Hunter reagent were purchased from Amersharm International plc. (Buckinghamshire, United Kingdom). The PDGF molecule consists of 2 peptide chains denoted A and B. Natural human PDGF consists of dimers of A and B chains (i.e., PDGF-AB, PDGF-BB and PDGF-AA). The A and B chains are approximately 60% homologous with one another in terms of their aminoacid sequence.[5] C-sis is the normal human cellular gene for B-chain PDGF, and the c-sis gene product has a structure equivalent to the PDGF B-chain homodimer. Anti-PDGF serum (a polyclonal preparation from goats immunized with homogenous human PDGF) was purchased from Collaborative Res (Bedford, Massachusetts).

IODINATION OF PLATELET-DERIVED GROWTH FACTOR: Recombinant PDGFc-sis was labeled with ^{125}iodine by the slightly modified Bolton-Hunter method.[6]

In these preparations, plasma PDGF levels were measured by radioimmunoassay. The variabilities of intra- and interassay for PDGF were 5.4 and 2.7%, respectively.

Statistical analysis: Plasma PDGF levels for each group are expressed as mean ± SD Comparison of the 3 groups was obtained by 1-way analysis of variance; if it was significant, Duncan's multiple range test[7] was performed. Probability values <0.05 were considered statistically significant.

RESULTS

Coronary angiographic findings: Eight patients with unstable angina had significant organic coronary artery stenosis ≥90% of luminal diameter in 2 or 3 major coronary arteries, 1 had angiographic evidence of intracoronary thrombus, and 5 had multivessel coronary artery spasm demonstrated in response to the intracoronary injection of acetylcholine.[8] Two patients with multivessel coronary spasm had 75% organic stenosis in 1 major coronary artery, and the other 3 had no significant organic stenosis. All patients with stable exertional angina had coronary artery stenosis ≥90% of luminal diameter in the major coronary arteries (10 in the left anterior descending coronary artery, 1 in the right coronary artery, and 4 in both the left anterior descending and right coronary arteries). The control patients had no significant coronary artery stenosis (<25% of luminal diameter), and no coronary spasm was demonstrated by the intracoronary injection of acetylcholine.[8]

Plasma platelet-derived growth factor levels in coronary sinus: The mean plasma PDGF level in the coronary sinus was significantly higher (p <0.01) in patients with unstable angina than in those with stable exertional angina and in control subjects (502.1 ± 98.7 vs 301.3 ± 62.5, and 312.7 ± 62.6 pg/ml). The levels were not significantly different between the stable exertional angina and control groups (Figure 1).

Plasma platelet-derived growth factor levels in aortic root: There were no significant differences in the mean plasma PDGF levels in the aortic root among the 3 groups (341.4 ± 98.2 pg/ml in the unstable angina group, 295.3 ± 73.9 in the stable exertional angina group, and 300.7 ± 40.8 in the control group; Figure 2).

DISCUSSION

It was proposed that PDGF, released at sites of vascular injury, has a significant role in the development of atherosclerosis, particularly with regard to the migration into and proliferation in the intima of vascular smooth muscle cells.[9] PDGF is also known to be a po-

FIGURE 1. Plasma platelet-derived growth factor (PDGF) levels in coronary sinus (pg/ml) in patients with unstable and stable exertional angina, and in control subjects. Values are mean ± SD. NS = not significant.

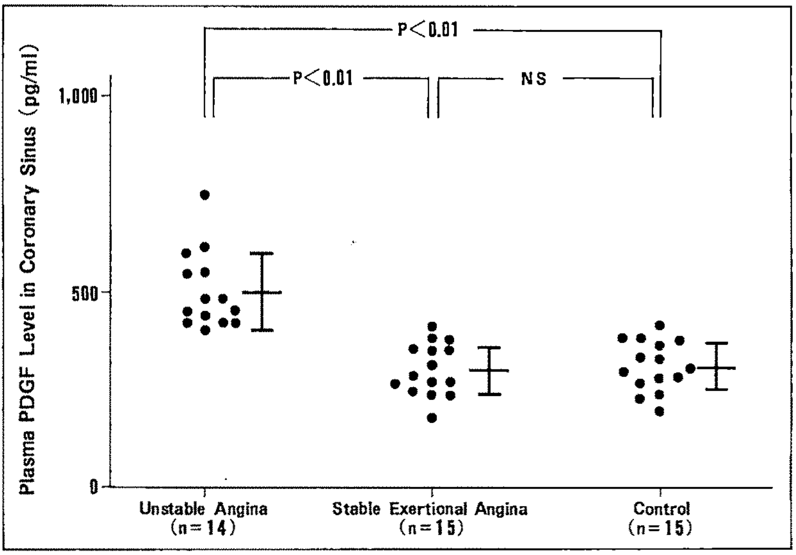
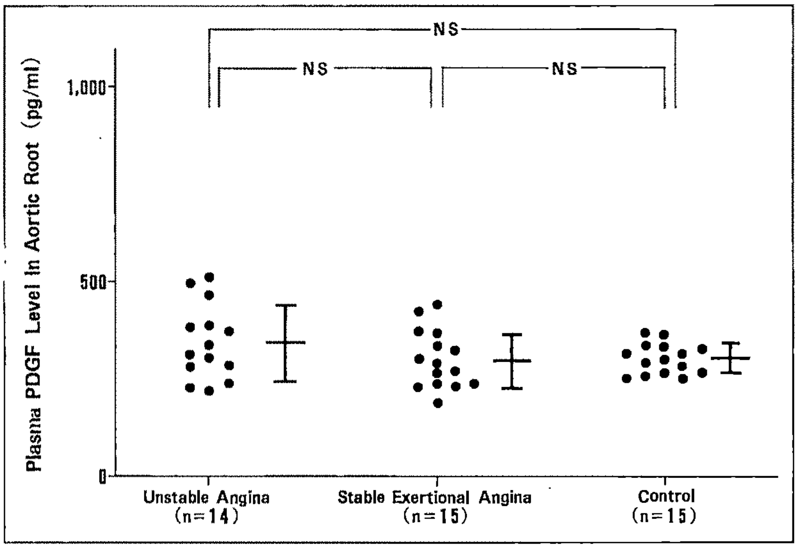


FIGURE 2. Plasma platelet-derived growth factor (PDGF) levels in aortic root (pg/ml) in patients with unstable and stable exertional angina, and in control subjects. Values are mean ± SD. NS = not significant.



tent vasoconstrictor. PDGF is more potent than angiotensin-II in inducing smooth muscle contraction and may play an important role in constriction of blood vessels in lesions of atherosclerosis.[4] These facts suggest an important pathophysiologic role of PDGF in unstable angina.

The 5 unstable angina patients with coronary artery spasm had multivessel coronary spasm. As we previously reported, the patients with multivessel coronary spasm had severe and prolonged angina, and their coronary arteries were normal or almost normal.[10-12]

We examined the plasma PDGF levels in the coronary sinus as well as in the aorta in patients with coronary artery disease. The mean plasma PDGF level in the coronary sinus was significantly higher in patients with unstable angina than in those with stable exertional angina and in control subjects. However, there were no significant differences in the mean plasma levels in the aortic root among the 3 groups. Thus, our data indicate that PDGF release is increased in the coronary circulation in patients with unstable angina.

It is known that fibrin forms and platelets adhere and are activated on the inner and outer surfaces of all known cardiac catheters.[13] Thus, local fibrin formation and platelet release on the catheter surfaces may cause the measurements obtained from blood collected through the catheters to be elevated artifactually. Furthermore, it is possible that the injection of radiographic contrast and heparin affects plasma PDGF levels. Because of these technical difficulties we obtained blood samples using catheters of the same quality and size by the same technique. The time intervals from catheter insertion to blood sampling were 15 minutes for all 3 groups. Furthermore, blood samples were collected from the coronary sinus and aortic root simultaneously at the same speed. Thus, our data provide information on directional changes in transcardiac PDGF generation.

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Platelet Function After In Vivo and In Vitro Treatment with Thrombolytic Agents

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Whereas in vitro studies showed that plasmin may induce both inhibition and activation of platelets, in vivo and ex vivo investigations suggested that thrombolytic agents are responsible for platelet stimulation. To gain further information on this topic, ex vivo platelet function was studied in 24 subjects with acute myocardial infarction treated with streptokinase or recombinant tissue-type plasminogen activator (rt-PA). Ten patients with acute myocardial infarction who did not receive thrombolytic treatment were also investigated. The data shows that at the end of thrombolytic infusion, the maximal extent of platelet aggregation and adenosine triphosphate release was reduced in treated patients compared with that in untreated ones. In subjects treated with streptokinase, the defect in platelet aggregation derived from both cellular and plasmatic defects. Plasmatic β-thromboglobulin concentration was significantly reduced after streptokinase, but unchanged after rt-PA. Three days after thrombolytic treatment, platelet aggregation of patients receiving streptokinase or rt-PA was not significantly different from that of untreated subjects. A similar defect in platelet function was obtained in vitro, incubating normal platelet-rich plasma with pharmacologic concentrations of streptokinase. Again, platelet function defect derived from both cellular and plasmatic damages. It cannot be excluded that platelet activation occurs in patients with acute myocardial infarction during the very early phases of thrombolytic treatment. However, it is suggested that a transient defect in platelet function follows both streptokinase and rt-PA infusion.

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Platelets play an important role in the development of myocardial infarction and are involved in both the initial response to thrombolytic therapy and the reocclusion that often follows successful thrombus lysis. It is well known that plasmin can modify platelet function and composition. However, whether this enzyme is responsible for platelet activation or inhibition is still subject to debate. In fact, in vitro and in vivo studies yielded conflicting results. Clinical studies using streptokinase[1,2] and recombinant tissue-type plasminogen activator (rt-PA)[3] suggested that fibrinolytic agents can be responsible for platelet activation, whereas in vitro studies showed that plasmin has no effect on platelet function,[4] and induces platelet hyper-[5–7] or hypofunction.[7,8–13] To obtain further information on this topic, we investigated ex vivo platelet function in patients with acute myocardial infarction undergoing thrombolytic treatment with streptokinase or rt-PA. In addition, to better understand the mechanisms of thrombolytic-dependent platelet dysfunction, we tried to reproduce in vitro the functional modification of platelets previously observed in vivo.

METHODS

Patients: Thirty-four patients with acute myocardial infarction (none receiving drugs that interfere with platelet function) were allocated to 1 of the following treatments within 6 hours from onset of clinical symptoms: (1) streptokinase (Streptase, Behringwerke AG, Marburg, Germany) — 1.5 × 10^6 U infused over 60 minutes (8 patients); (2) streptokinase — 1.5 × 10^6 U over 60 minutes, followed by intravenous heparin (Eparina Vitrum, Bonomelli Divisione Farmaceutici, Dolzago, Italy) (bolus of 1,000 U, followed by 1,000 U/hour) (9 patients); or (3) rt-PA (Actilyse, Boehringer Ingelheim, Ingelheim am Rhein, Germany) administered as a 10 mg bolus, followed by an infusion of 50 mg over the first hour and then 20 mg over each of the subsequent 2 hours. At the end of rt-PA therapy, heparin infusion (as described previously) was begun (8 patients). Ten patients with acute myocardial infarction who did not receive thrombolytic and heparin treatment owing to the risk of bleeding were also investigated. Drugs known to interfere with platelet function (other than thrombolytic agents) were not used. Platelet function was studied before treatment, at the end of drug infusion, and 6, 24, 48, 72 and 96 hours after the beginning of treatment. Patients not receiving thrombolytic drugs were studied at similar time intervals after onset of symptoms.

Ex vivo and in vivo studies: Blood samples were obtained from the antecubital vein without stasis and anti-

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coagulated with 3.8 g/dl of sodium citrate (blood/anticoagulant, 9/1). Platelet-rich and platelet-poor plasma were obtained by centrifuging the blood at 200 g for 10 minutes and at 4,500 g for 20 minutes, respectively, at room temperature. Platelet-rich plasma was adjusted with platelet-poor plasma to 250 × 10^9 platelets/liter.

Platelet aggregation after adenosine diphosphate (Sigma Chemical Company, St. Louis, Missouri), collagen and ristocetin (Mascia Brunelli, Milan, Italy) was studied by the densitometric method of Born[14] with a Chrono-Log Lumi-Aggregometer (Chrono-log Corporation, Havertown, Pennsylvania). In some patients receiving streptokinase, platelet-rich plasma containing 150 × 10^9 platelets/liter was prepared mixing appropriate amounts of platelet-rich plasma obtained before thrombolytic therapy with platelet-poor plasma obtained at the end of streptokinase infusion, and vice versa. Then, platelet aggregation was studied as described previously.

Adenosine triphosphate release was studied by the "luciferase-luciferin method."[15] Luciferase-luciferin was obtained from Chrono-log Corporation. Preliminary experiments showed that streptokinase (1,000 U/ml) did not interfere with adenosine triphosphate assay. Platelet aggregation and release reaction studies were completed within 60 minutes from blood sampling.

Beta-thromboglobulin content of plasma was determined by a commercial immunoassay (ELISA β-TG, Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany). Blood was collected with the anticoagulant (citrate, theophylline, adenosine and dipyridamole) supplied by the manufacturer, with the addition of 200 KIU/ml of aprotinin (Trasylol, Bayer, Leverkusen, Germany). Preliminary experiments showed that streptokinase (1,000 U/ml) did not interfere with the assay.

In vitro studies: Blood was obtained from healthy subjects who denied drug consumption, and platelet-rich plasma was obtained as described previously. Platelet-rich plasma was incubated with different amounts of streptokinase at 37°C for varying periods of time. At the end of incubation, aprotinin (200 KIU/ml) and ϵ-aminocaproic acid (10 μM) (Sigma) were added. When required, plasmin inhibitors were added to platelet-rich plasma together with streptokinase. In control experiments, platelet-rich plasma was incubated without streptokinase. In some experiments, after 1 hour of incubation with streptokinase (1,000 U/ml), plasmin inhibitors were added, platelets were washed 3 times with HEPES buffer (145 mmol of sodium chloride, 5 mmol of potassium chloride, 1 mmol of magnesium sulfate, 10 mmol of HEPES, and 5 mmol of glucose) and resuspended in normal platelet-poor plasma obtained from the same donor. Alternatively, platelet-rich plasma was incubated without streptokinase for 60 minutes at 37°C, platelets were washed as reported previously, and finally resuspended in platelet-poor plasma incubated for 1 hour at 37°C with 1,000 U/ml of streptokinase (aprotinin and ϵ-aminocaproic acid were added at the end of incubation). In control experiments, streptokinase was not present during platelet-rich or platelet-poor plasma incubation. Platelet aggregation was studied by Born's method.[14] Agonist's concentrations inducing 50% aggregation (maximal extent) in control platelets were used. Adenosine triphosphate release was studied as reported previously.

For the study of intracellular calcium ion (Ca^{++}) increase, platelets were loaded with the photoprotein aequorin (Chrono-log) by the dimethyl sulfoxide method,[16] and finally resuspended in normal platelet-poor plasma. Then, platelets were stirred for 30 minutes at 37°C in the presence of 1,000 U/ml of streptokinase in a "platelet ionized calcium aggregometer" (Chrono-log), and light emission was recorded.

Statistical analysis: The statistical significance of the differences was determined by paired or unpaired *t* test, or by multiple comparison procedure (Scheffè test). "Normal range" was represented by the mean ± 2 standard deviations of the values observed in 30 healthy subjects.

RESULTS

Ex vivo and in vivo studies: At hospital admission, the maximal extent of platelet aggregation and adenosine triphosphate release in patients with acute myocardial infarction was always within the normal range. Before treatment, no significant difference in platelet function was observed among different groups of patients. Table I shows ex vivo platelet aggregation after thrombolytic treatment. No significant differences were observed between patients who underwent heparin therapy and those who did not (data not shown). Figure 1 shows the results of "cross over studies," indicating that the defect of platelet aggregation after collagen mainly derived from a cellular defect, whereas both cellular and plasmatic modifications were responsible for defective response to adenosine diphosphate.

Beside platelet aggregation, adenosine triphosphate release was also reduced after streptokinase and rt-PA. However, normal release reaction was observed when platelets were stimulated by high doses of collagen (Table II).

At hospital admission, plasmatic β-thromboglobulin level was higher than normal in 11 patients (healthy subjects 16.6 ± 3.0 IU/ml, patients 24.0 ± 7.0 IU/ml; $p < 0.05$). Successively, no significant modifications with respect to basal values were observed in control and rt-PA patients (data not shown). On the contrary, a significant reduction of β-thromboglobulin levels (66 ± 20% of basal values) was observed at the end of streptokinase infusion.

In vitro studies: Incubation with streptokinase (100 to 5,000 U/ml) greatly reduced platelet aggregation (Table III). The addition of plasmin inhibitors to platelet-rich plasma largely prevented the inhibition of platelet aggregation (data not shown) Streptokinase (1,000 U/ml) impaired release reaction also. At the end of 1 hour of incubation, adenosine triphosphate release after adenosine diphosphate (5 μM) and collagen (2 μg/ml) was 3.4 ± 7.6 and 37.1 ± 13.0% of basal values, respectively. Both these values were significantly different from those of control (platelets incubated without streptokinase). However, platelets retained the ability to undergo release reaction after stimulation with high-dose collagen (adenosine triphosphate release induced by 20 μg/ml of collagen 95.0 ± 13.5% of basal values). Figure 2 shows the time course of agonist-induced platelet aggregation during incubation with 1,000 U/ml of streptokinase. When streptokinase (1,000 U/ml) was added to stirred platelet-rich plasma, we never observed platelet aggregation, adenosine triphosphate release or Ca^{++} transient. Table IV describes the results of "cross over" studies.

DISCUSSION

Thrombolytic agents are able to recanalize occluded coronary arteries and reduce mortality of patients affected by acute myocardial infarction.[17,18] Recent evidence suggests that the mechanism of action of these drugs is more complex than previously believed. In fact, in addition to activating fibrinolysis, they profoundly

TABLE I Ex Vivo Platelet Aggregation* at Different Times After Beginning of Thrombolytic Therapy with Streptokinase and rt-PA

Hours After Therapy	Adenosine Diphosphate—Induced Aggregation (5 μM)			Collagen—Induced Aggregation (2 μg/ml)			Ristocetin—Induced Aggregation (1.5 mg/ml)		
	Contro	Sk	rt-PA	Control	Sk	rt-PA	Control	Sk	rt-PA
1 to 3	113 ± 20	36 ± 34†	69 ± 53†	95 ± 15	40 ± 36†	76 ± 50	104 ± 22	72 ± 45†	91 ± 49
		†			†				
6	124 ± 12	55 ± 35†	66 ± 33†	105 ± 38	60 ± 41†	50 ± 41†	87 ± 23	85 ± 48	109 ± 43
24	122 ± 12	70 ± 37†	117 ± 45	104 ± 33	83 ± 33	80 ± 39	97 ± 22	90 ± 31	101 ± 37
48	106 ± 21	72 ± 45†	101 ± 47	104 ± 39	91 ± 22	79 ± 12†	104 ± 9	103 ± 23	102 ± 43
72	89 ± 13	80 ± 37	95 ± 32	98 ± 38	91 ± 26	87 ± 24	104 ± 22	102 ± 14	81 ± 33
96	90 ± 8	90 ± 30	91 ± 44	101 ± 26	104 ± 31	92 ± 27	95 ± 22	98 ± 13	88 ± 26

*Maximal extent of platelet aggregation, expressed as % with respect to pretreatment values (absolute values of platelet aggregation before therapy were the following: after adenosine diphosphate 68 ± 20; after collagen 72 ± 18; and after ristocetin 79 ± 17).

†$p < 0.05$.

The statistical significance of the differences between treated and control patients is reported, as well as the statistical significance of the difference between streptokinase and rt-PA patients.

rt-PA = recombinant tissue-type plasminogen activator; Sk = streptokinase.

TABLE II Platelet Release Reaction (adenosine triphosphate release)* at End of Thrombolytic Therapy

Stimulating Agent	Control	Streptokinase	rt-PA
Adenosine diphosphate (5 μM)	89 ± 22	47 ± 39†	61 ± 32†
Collagen (2 μg/ml)	96 ± 12	37 ± 38†	103 ± 23
Collagen (20 μg/ml)	98 ± 25	111 ± 34	108 ± 22

*% of pretreatment values (absolute values of adenosine triphosphate release at hospital admission: after 5 μM adenosine diphosphate 1.49 ± 1.00 μM; after 2 μg/ml collagen 1.53 ± 0.97). Control subjects were studied at corresponding time intervals after onset of symptoms.

†$p < 0.05$ with respect to control.

rt-PA = recombinant tissue-type plasminogen activator.

TABLE III Platelet Aggregation* in Platelet—Rich Plasma After In Vitro Incubation with Different Amounts of Streptokinase

Streptokinase (U/ml)	Platelet Agonist		
	Collagen	Adenosine Diphosphate	Ristocetin
100	29 ± 42†	40 ± 34†	37 ± 30†
1,000	31 ± 31†	41 ± 27†	32 ± 32†
5,000	46 ± 34†	40 ± 19†	41 ± 22†

*% aggregation with respect to control platelets (incubated without streptokinase). Each value represents mean ± standard deviation of 5 experiments.

†$p < 0.05$ with respect to control.

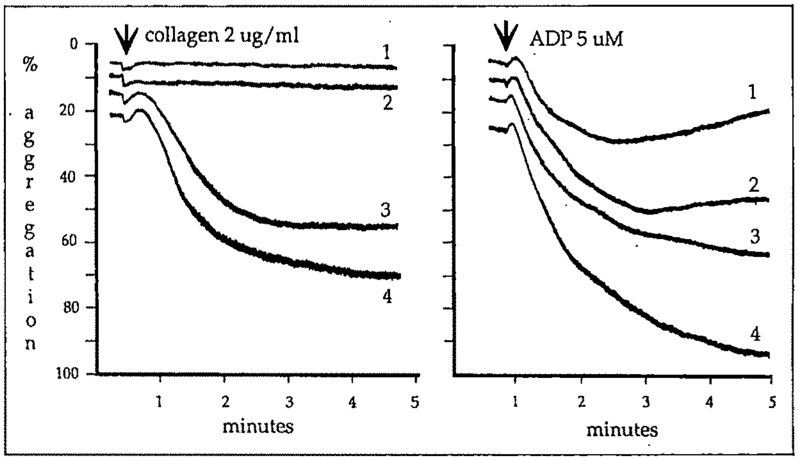

FIGURE 1. "Cross over" studies. Platelet aggregation of patients with acute myocardial infarction was studied in platelet-rich plasma containing 150 × 10^9 platelets/liter, and prepared mixing (1:1) platelet-rich and platelet-poor plasma obtained before and after streptokinase treatment. Similar results were obtained in 2 different patients at 2 different occasions. ADP = adenosine diphosphate; 1 = poststreptokinase platelet-rich + platelet-poor plasma; 2 = poststreptokinase platelet-rich + prestreptokinase platelet-poor plasma; 3 = prestreptokinase platelet-rich + poststreptokinase platelet-poor plasma; 4 = prestreptokinase platelet-rich + platelet-poor plasma.

TABLE IV Aggregation* of Platelets Incubated for One Hour at 37°C With or Without Streptokinase (1,000 U/ml) After Washing and Resuspension in Streptokinase–Treated or Untreated Platelet–Poor Plasma

Agonist	Plt + Sk PPP + Sk	Plt + Sk PPP − Sk	Plt − Sk PPP + Sk
Adenosine diphosphate	22 ± 13†	54 ± 9†	45 ± 21†
	†	NS	
Collagen	34 ± 38†	33 ± 8†	77 ± 10
	NS	†	
Ristocetin	47 ± 22†	46 ± 20†	120 ± 33
	NS	†	

*% aggregation with respect to control (platelets incubated without streptokinase, washed and resuspended in platelet–poor plasma incubated without streptokinase). Each value represents the mean ± standard deviation of 4 experiments.

†p <0.05.

The statistical significance of differences between control and streptokinase–treated samples is reported beside each value. The statistical significance of differences between treated samples is also reported.

NS = not significant (p >0.05); Plt = platelets; PPP = platelet–poor plasma; Sk = streptokinase.

modify the coagulation system, promoting both anti- and prothrombotic effects. Reduction of fibrinogen,[19-21] factors V[22] and VIII,[23] together with an increase in fibrinogen/fibrin degradation products,[21,24] could promote an antithrombotic effect. On the contrary, thrombin formation[25] and late qualitative and quantitative fibrinogen modifications[26] could exert a prothrombotic effect. The degree of these modifications differs according to the type of thrombolytic agent used. Knowledge of the systemic effects of thrombolytic drugs may be valuable in selecting treatment after thrombolysis to reduce the occurrence of coronary reocclusion without increasing the risk of bleeding.

Despite platelet involvement in the bleeding/reocclusion risk, there is little information regarding the effect of thrombolytic agents on platelet function. In vitro studies demonstrated that plasmin can inhibit,[7,8-13] stimulate[5-7] or have no effect on platelets.[7] In vivo investigations showed that streptokinase and rt-PA infusion was followed by both the increase in plasmatic β-thromboglobulin concentration[2] and urinary excretion of stable thromboxane metabolites,[1,3] indicating platelet activation, and by prolongation of bleeding time,[27] indicating platelet inhibition.

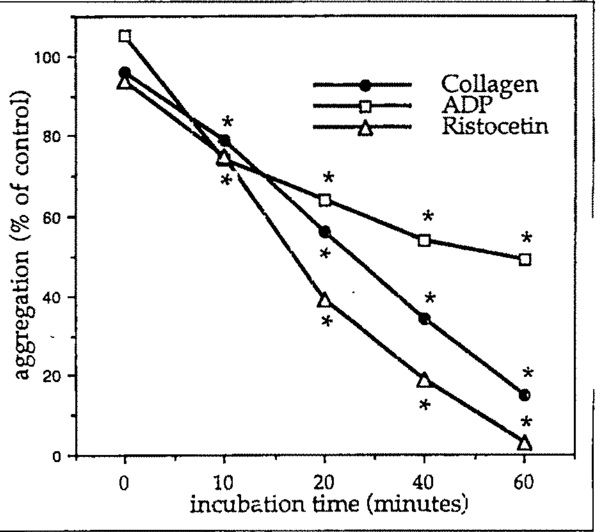

FIGURE 2. Platelet aggregation induced by collagen, adenosine diphosphate (ADP) and ristocetin after different incubation times of platelet-rich plasma with 1,000 U/ml of streptokinase. Platelet aggregation is expressed as % with respect to platelet-rich plasma incubated without streptokinase for same times. Mean ± standard deviation of 4 experiments. *p <0.05 with respect to control.

To obtain further information on this topic, we investigated platelet function in patients with acute myocardial infarction receiving streptokinase or rt-PA. The results of ex vivo studies demonstrated that transient inhibition of platelet function follows thrombolytic therapy. The degree of this inhibition was greater with streptokinase than with rt-PA. Moreover, streptokinase treatment significantly reduced β-thromboglobulin plasmatic concentration, whereas rt-PA did not. Similar inhibition of platelet aggregation and release reaction was observed after in vitro incubation of platelets with pharmacologic concentrations of streptokinase. In addition, incubation of platelets with 1,000 U/ml of streptokinase never induced platelet aggregation, adenosine triphosphate release or Ca^{++} transient. Therefore, our experience clearly shows that in vivo and in vitro thrombolytic treatment may be responsible for significant inhibition of aggregation and release reaction. In our opinion, the defect in adenosine triphosphate secretion after adenosine diphosphate and low-dose collagen was a consequence of the aggregation defect, because it is well known that release reaction in platelet-rich plasma is largely dependent on aggregation.[28] This hypothesis is also supported by the observation that platelets underwent normal adenosine triphosphate secretion after stimulation with high doses of collagen.

The in vitro inhibitory effect of streptokinase we observed confirms and extends the conclusions of other investigators,[7,8-13] but disagrees with the results of Schafer et al[6] and Niewiarowski et al[5] who described plasmin-induced platelet activation. These differences can be simply explained by stating that platelet stimulation was observed by the investigators using high plasmin concentration (>1 CU/ml),[5,6] whereas platelet inhibition was observed when lower plasmin concentrations were used or when activation of fibrinolysis was achieved in platelet-rich plasma by thrombolytic drugs.[7-13] The different results obtained by Rao et al,[4] who observed no effect of thrombolytic drugs on platelet aggregation, probably derived from different durations of incubation (10 minutes in the Rao experiments, and 60 minutes in our experimental conditions).

Our in vivo results agree with those of Gimple et al[27] who observed prolonged bleeding time after rt-PA infusion. We have no explanation for the different results obtained by Udvardy et al[2] who observed increased concentrations of β-thromboglobulin in platelet-poor plasma after streptokinase treatment. On the contrary, we believe that our results are not in contrast with those of Fitzgerald et al[1] and Kerins et al[3] In fact, the study of urinary concentration of thromboxane metabolites may detect a very early and transient platelet activation during thrombolysis. Furthermore, the study of plasmatic concentration of β-thromboglobulin 1 to 3 hours after beginning therapy may be unable to detect this phenomenon owing to the very short plasmatic half-life of this compound.[29] Therefore, combining our data with those of Fitzgerald and Kerins leads us to hypothesize that both platelet activation and inhibition occur during thrombolytic treatment and that platelet activation occurs during the very early periods of thrombolytic treatment (formation of thrombin? re-exposure of the ruptured atherosclerotic plaque? direct platelet activation by peak plasma plasmin concentration?), whereas inhibition of platelet function occurs later. The data of Rudd et al,[30] obtained from rabbits treated with thrombolytic drugs, support this hypothesis; in fact, shortly after the beginning of infusion, they observed ex vivo platelet hyperfunction, whereas platelet hypofunction occurred later.

Our data are not sufficient to determine the mechanism of platelet dysfunction. However, "cross over" studies after in vivo and in vitro streptokinase treatments clearly showed that the damage was complex, deriving from both cellular and plasmatic defects. Previous reports regarding cellular defect demonstrated that plasmin caused an artifactual cleavage of platelet glycoprotein receptors in the absence of extracellular Ca^{++}, whereas this phenomenon did not take place in citrated plasma.[31] Since we studied platelet function in samples anticoagulated with sodium citrate, we believe that such an artifact was not responsible for the platelet dysfunction we observed. Therefore, further investigations are needed to identify the mechanism of the cellular defect. The results we obtained are at variance with those of Torr et al[13] who demonstrated that rt-PA-induced functional defect of platelets derived entirely from the presence of fibrinogen degradation products in plasma. These data, together with the observation of Fears et al,[12] suggest that the effect of streptokinase and rt-PA on platelets may be different from both a qualitative and a quantitative point of view.

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Identification of Patients at High Risk for Recurrence of Sustained Ventricular Tachycardia After Healing of Acute Myocardial Infarction

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A prognostic index for nonfatal recurrences of ventricular tachycardia (VT) was developed using a retrospective analysis of a group of 206 patients with sustained monomorphic VT or ventricular fibrillation (VF) after healing of acute myocardial infarction. 74 patients (36%) (64 with VT and 10 with VF) had recurrences of sustained monomorphic VT during 3.4 $\pm$ 9 years of follow-up. Three clinical variables were selected and weighted by stepwise logistic discriminant analysis of the study group. They were coded as follows: interval of myocardial infarction to arrhythmia (<2 months = 1; 2 to 6 months = 2; >6 months = 3), drug therapy with or without sotalol (with = 1, without = 2), and VT or VF as the presenting arrhythmia (VT = 1, VF = 2). The prognostic index was: $3.41 - (0.56 \times \text{interval}) - (1.94 \times \text{therapy}) + (0.86 \times \text{arrhythmia})$. This index was validated prospectively in a test group of 158 consecutive patients with VT or VF after healing of acute myocardial infarction. Patients were allocated into different classes with decreasing prognostic index values associated with increasing risk for recurrences of VT. In the test group, 27 of 158 (17%) patients (22 with VT and 5 with VF) had recurrences of VT (follow-up of 2 $\pm$ 2 years). Two risk classes of patients were identified: high risk for recurrences of VT (61%) corresponding to patients with a negative index; and low risk (4%) consisting of those with a positive index. Thus, using 0 as the cutoff point, the sensitivity, specificity, and positive and negative predictive values were 81, 89, 62 and 96%, respectively. This prognostic index may be used in selecting treatment for patients with severe ventricular arrhythmias after healing of acute myocardial infarction.

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Electrophysiologic testing has been reported to be of value in predicting survival in patients with ventricular tachyarrhythmia[1] and in those resuscitated from out-of-hospital cardiac arrest.[2–4] Less attention has been given to the identification of patients at high risk for recurrence of nonfatal ventricular tachycardia (VT) after healing of acute myocardial infarction.[5] The present study was precisely aimed at evaluating clinical information likely to discriminate between patients at low risk and those at high risk of developing recurrences of VT after healing of acute myocardial infarction. By retrospective analysis of VT/ventricular fibrillation (VF) patients with and without currences of VT, a prognostic index was developed for identifying patients with VT/VF after healing of acute myocardial infarction at high risk of recurrences of VT in the future. Thereafter, the value of this prognostic index was tested in a different group of patients with the same clinical problem.

METHODS

The study group (Maastricht, the Netherlands) comprised 206 consecutive patients (172 men and 34 women, mean age 59 $\pm$ 9 years, range 38 to 79) with a healed myocardial infarction (154 with electrocardiographically documented sustained monomorphic VT and 52 with VF). In all patients the first episode of arrhythmia occurred >3 days after infarction. The test group consisted of 158 consecutive patients (149 men and 9 women, mean age 59 $\pm$ 8 years, range 27 to 81; 80 patients with sustained monomorphic VT and 78 with VF). They were admitted to the University Hospital of Heidelberg, Germany, during the same time period as the Maastricht patients. In addition to history and physical examination, data were available on exercise testing, coronary and left ventricular angiography, and programmed electrical stimulation. Left ventricular ejection fraction was measured either invasively (85%) or noninvasively (15%) (echocardiography or nuclear). As previously reported from our institution, there is a good correlation between the echocardiographic, angiographic and nuclear determination of the ejection fraction.[6] Left ventricular aneurysm was defined as ≥ 1 circumscribed segment of dyskinesia identified by either contrast ventriculography or echocardiography.

All patients received antiarrhythmic drug therapy. No patient had arrhythmia surgery or an implantable defibrillator. In the study group, therapy was given while the "Parallel approach" was followed. This approach was described in detail elsewhere.[7] Briefly, pa-

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tients admitted with an episode of VT or VF were continuously monitored in the coronary care unit. After washout of antiarrhythmic drug therapy (if present) patients underwent baseline studies including exercise testing, echocardiography and programmed electrical stimulation. These tests were repeated after institution of antiarrhythmic drug therapy, which was selected empirically. Antiarrhythmic therapy was continued until a spontaneous recurrence of the ventricular arrhythmia was observed. Inducibility of an arrhythmia during programmed electrical stimulation did not influence the antiarrhythmic drug regimen. Only spontaneous recurrence of VT/VF during the treatment period was reason to change the antiarrhythmic drug regimen. In the test group, antiarrhythmic drug selection was based on serial drug testing.[8]

Statistical analysis: Seven clinical and 4 nonclinical variables were coded. They were: age, history of >1 myocardial infarction, New York Heart Association class for angina, anterior location of myocardial infarction, time interval from myocardial infarction to first spontaneous arrhythmia (sustained VT or VF) coded from 1 to 3 (arrhythmia present <2 months = 1; 2 to 6 months = 2; and >6 months = 3), type of arrhythmia (VT or VF) (VT = 1, and VF = 2) and antiarrhythmic drug therapy administered (amiodarone, propafenone, sotalol or procainamide) (sotalol = 1, and no sotalol = 2), left ventricular ejection fraction, number of coronary arteries involved, presence or absence of left ventricular aneurysm, and finally, existence of an exercise-related arrhythmia.

The study group (206 patients) was used to select the most discriminating variables and establish a prognostic index. Thereafter, the performance of this index was validated on the test group (158 patients). Age and left ventricular ejection fraction were analyzed as continuous variables. Data were first screened by univariate analysis for differences between patients with and without recurrences of VT. Quantitative variables were tested by *t* test and nominal findings by the chi-square test. To discriminate between patients with and without recurrences of VT on a multivariate level, the multiple group logistic discrimination method was used.[9] Variables were selected in a stepwise manner using a likelihood ratio criterion distributed as a chi-square test on 1 degree of freedom. All results were considered to be significant at the 5% level.

RESULTS

In the study group, 74 of 206 (36%) patients (64 and 10 from the sustained VT and VF groups, respectively) had recurrences of VT after a mean follow-up of 3.4 ± 9 years. In the test group, 27 of 158 (17%) patients (22 and 5 from the sustained VT and VF groups, respectively) had recurrences of VT after a mean follow-up of 2.4 ± 2 years. In the study group, 15 patients (7%) and in the test group, 34 (21%) were receiving oral sotalol (80 to 420 mg). Of patients receiving sotalol, recurrences of sustained monomorphic VT were observed in 2 (13%) in the study group and in 4 (12%) in the test group. A comparison of the clinical and nonclinical variables in the 2 patient populations is listed in Table I.

TABLE I Characteristics of the Two Groups of Patients

	Study Group	Test Group	p Value
No. of pts.	206	158	
Age (mean yr)	59	59	NS
Men/women	172/34	149/9	<0.003
Anterior MI	73 (35%)	86 (54%)	<0.001
Multiple MI	45 (29%)	50 (31%)	NS
LV aneurysm	99 (48%)	64 (40%)	NS
LV ejection fraction (mean)	35 ± 11	38 ± 10	<0.02
3-vessel disease	51 (24%)	39 (24%)	NS
VT	154 (74%)	81 (51%)	<0.001
VF	52 (36%)	77 (48%)	<0.0001
Sotalol	15 (7%)	34 (21%)	<0.001
Interval of MI to arrhythmia			
<2 months	98 (47%)	58 (28%)	<0.04
>2 months	108 (52%)	100 (63%)	NS
Exercise-related arrhythmia	17 (8%)	21 (13%)	NS

LV = left ventricular; MI = myocardial infarction; NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia.

Prognostic value of the clinical variables: In the study group, the stepwise variable selection procedure was used for the 7 clinical and 4 nonclinical variables. Using this approach, 3 clinical variables were retained as the most predictive of recurrences of VT after healing of acute myocardial infarction. The time interval from myocardial infarction to first episode of VT or VF was selected first, having the most powerful prognostic value (<2 months = 1; 2 to 6 months = 2; and >6 months = 3; $p < 0.001$). It was followed by used sotalol as the antiarrhythmic drug (sotalol = 1, and no sotalol = 2; $p < 0.007$), and VT as the presenting arrhythmia (VT = 1, and VF = 2; $p < 0.002$). From these 3 clinical variables, a risk index was derived using the following equation: 3.41 − (0.56 × time interval of myocardial infarction to VT/VF) − (1.94 × sotalol [yes or no]) + (0.86 × VT or VF). Negative values (<0) were associated with a high risk of recurrences of VT, whereas positive values (>0) predicted a favorable development. For example, if a patient has VT as presenting arrhythmia (code = 1) 6 months after myocardial infarction (code = 3) and receives another antiarrhythmic drug than sotalol (code = 2), the prognostic index for recurrences of VT is −1.29 (negative value, high risk for VT recurrences). None of the nonclinical variables were related to recurrences of VT.

Validation of the prognostic index: The index obtained in the study group was used for the test group of 158 patients. Of the 36 patients (23%) with a negative index (high risk for VT recurrences), 22 (61%) actually had recurrences of VT. Of the 122 patients (77%) with a positive index (low risk for VT), only 5 (4%) had recurrences of VT. In terms of sensitivity, specificity, and positive and negative predictive values, the index had the following results: 81, 89, 62 and 96%, respectively.

DISCUSSION

Several studies using invasive parameters attempted to find predictors for death in patients with sustained VT or cardiac arrest.[1-4] The objective of our study was to (1) establish a prognostic index for recurrences of sustained monomorphic VT in patients with VT or VF after a previous myocardial infarction from clinical and laboratory findings, and (2) validate this prognostic index in a test group.

In our study, 3 clinical variables were selected from stepwise logistic discriminant analysis: (1) time interval from myocardial infarction to sustained VT or VF, (2) sotalol as antiarrhythmic drug, and (3) VT as presenting arrhythmia. These clinical variables were found to be more predictive for recurrences of VT than were invasive variables or the occurrence of a ventricular arrhythmia during exercise testing.

A prognostic index based on the variables selected was validated in a test group, allowing us to identify high-risk patients with a predictive value >60%.

Selection of antiarrhythmic drug treatment was different in the 2 groups of patients. The "Parallel approach" was used in the study group, and serial drug testing in the test group. However, irrespective of the approach used, the prognostic index was able to recognize patients at high and low risks for recurrences of sustained monomorphic VT in both the study and test groups.

Importance of the time interval between myocardial infarction and the first episode of arrhythmia: The interval from myocardial infarction to the first episode of sustained ventricular arrhythmia was the best indicator of recurrence of sustained monomorphic VT. We previously showed that a time interval <2 months between myocardial infarction and the appearance of sustained ventricular arrhythmia is a good predictor for identifying patients with a high mortality after myocardial infarction.[10] In another study[5] we indicated that the value of this variable in detecting patients at high risk of sudden death after myocardial infarction can be further augmented by adding other clinical variables such as the occurrence of circulatory arrest during the first episode of sustained spontaneous ventricular arrhythmia, New York Heart Association functional class III for dyspnea, and presence of >1 previous myocardial infarction.

Value of sotalol as the antiarrhythmic drug used: Sotalol, a β-blocking agent with class III antiarrhythmic properties, has been shown to be of short- and long-term benefit in the management of life-threatening ventricular arrhythmias.[11-14] Nademanee et al[11] observed that both the prevention of reinduction of VT/VF by intravenous sotalol and the suppression of spontaneously occurring arrhythmias by the oral drug were predictive of long-term drug efficacy.

Ruder et al[12] studied 65 patients with symptomatic previously drug refractory sustained VT/VF treated with oral sotalol (80–420 mg) and found an arrhythmia-free incidence at 6- and 12-month follow-up of 54 and 47%, respectively.

Ventricular tachycardia as the presenting arrhythmia: This variable augmented the ability to recognize risk for recurrences of sustained VT. In our study population, patients who had VT (154 patients) as the presenting arrhythmia had a higher incidence of recurrences of VT (41%) than did those with VF (52 patients [19%]; p <0.03).

In the VT group, 14 patients were receiving sotalol, and only 2 of these had recurrences of VT. In the VF group, only 1 patient was receiving sotalol, and did not have recurrences of VT.

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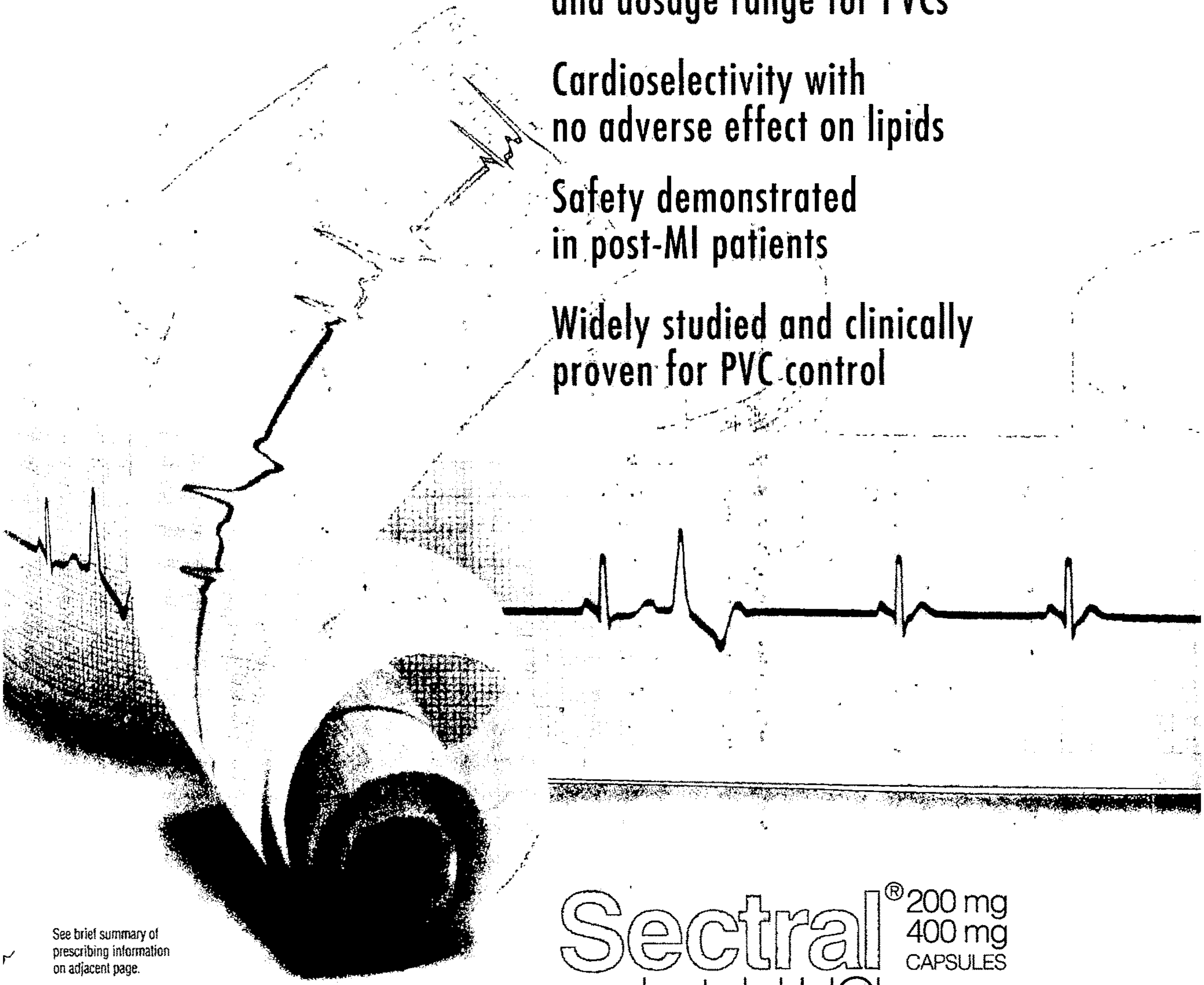

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CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β_1-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%; *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Correlation of the Complete Version of the Selvester QRS Scoring System with Quantitative Anatomic Findings for Multiple Left Ventricular Myocardial Infarcts

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Steven L. Peck, MS, Eileen M. Mikat, PhD, Raymond E. Ideker, MD, PhD,
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Ronald H. Selvester, MD, and Galen S. Wagner, MD

The correlation between myocardial infarct size estimated by the complete version of the Selvester QRS scoring system and that documented by pathoanatomic studies has been reported for single anterior, inferior and posterolateral infarcts. Although previous studies described electrocardiographic changes in patients with multiple infarcts, no quantitative documentation of the ability of such changes to estimate the total amount of left ventricular infarction has been reported. This study of 32 patients with anatomically documented multiple infarcts shows a significant correlation between QRS-estimated and anatomically documented sizes ($r = 0.44$; $p = 0.01$), which is less than that previously reported for single infarcts in the anterior, inferior and posterolateral locations. Several of the 54 electrocardiographic criteria were never satisfied. Criteria for posterior infarction were seldom present, suggesting "cancellation effect" of coexisting anterior infarction. These results will be the basis for future modification of QRS criteria for estimating myocardial infarct size.

(Am J Cardiol 1992;69:465–469)

With the advent of thrombolytic therapy there is now a major focus on limiting the size of acute myocardial infarcts.[1,2] Several clinical techniques[3,4] including serum enzymes, and scintigraphic and magnetic resonance imaging[5] have been used to evaluate the functional and anatomic extent of single and multiple myocardial infarcts. Previous studies documented the correlation between the Selvester QRS scoring system applied to the standard 12-lead electrocardiogram and anatomically measured percent left ventricular infarction in patients with single anterior,[6] inferior[7] and posterolateral[8] locations. There has been no quantitative documentation of the ability of this scoring system to estimate the sizes of multiple infarcts. Previous studies demonstrated that QRS-waveform cancellation confounds the diagnosis of multiple infarcts,[9,10] and it is important to determine the effect of such cancellation on estimation of cumulative infarct size. This study aims to: (1) correlate the total percentage of left ventricular infarction measured anatomically in patients with multiple infarcts with that estimated by the complete 54-criteria 32-point Selvester QRS scoring system[11,12]; and (2) determine the sensitivities of each of the 54 criteria in identifying the infarcts present.

METHODS

Patient population: Deceased patients evaluated at the Duke University and Johns Hopkins cardiovascular pathology laboratories between 1975 and 1988, and from the Multicenter Investigation of Limitation of Infarct Size (MILIS)[13] were included in this study if they had: (1) ≥2 acute or healed infarcts that were anatomically distinguishable; (2) no evidence of left ventricular rupture, surgical resection of the left ventricle (LV), or valvular repair; and (3) an electrocardiogram obtained after the final infarct that did not show confounding factors such as ventricular hypertrophy, bundle branch or fascicular block, electrolyte imbalance or pericarditis. For patients with only completely healed infarcts anatomically, the final electrocardiogram during the year before death was used. Patients with an acute infarct immediately before death were included provided that the infarct was anatomically distinguishable and quantifiable, and that there was an electrocardiogram available that met the criteria outlined previously.

From the Departments of Pathology and Medicine, Duke University Medical Center, Durham, North Carolina, the Multicenter Investigation of Limitation of Infarct Size (MILIS) Study Group (Barnes Hospital, St. Louis, Missouri; Massachusetts General Hospital, Boston, Massachusetts; Medical Center Hospital of Vermont, Burlington, Vermont; Brigham and Women's Hospital, Boston, Massachusetts; and Parkland Memorial Hospital, University of Texas Health Science Center, Dallas, Texas), and the Johns Hopkins Hospital, Baltimore, Maryland. Manuscript received February 8, 1991; revised manuscript received and accepted October 25, 1991.

Address for reprints: Galen S. Wagner, MD, Duke University Medical Center, Box 3636, Durham, North Carolina 27710.

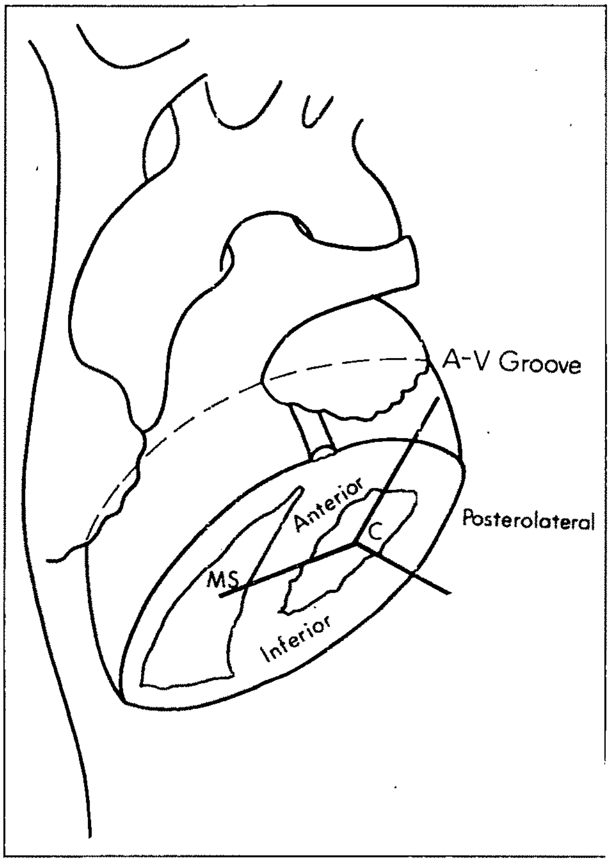


FIGURE 1. Division of left ventricle into anterior, inferior and posterolateral thirds. *The line MS-C* bisects septal sector. A-V = atrioventricular; C = centroid of epicardial outline and right septal border; MS = reference point in midseptum.

Thirty-two patients (19 men [59%], mean age 61 years [range 42 to 77], and 13 women [41%], mean age 63 years [range 35 to 80]) met the criteria for inclusion in the study. Six patients had 3 distinct infarcts, whereas the other 26 had 2 distinct infarcts. The interval between the initial and final infarctions ranged from 22 days to 23 years.

Anatomic techniques: Hearts were prepared and studied as described previously.[14] The LV was divided in thirds by drawing a line from its centroid to the midpoint of the interventricular septum (Figure 1). From this reference, the LV was divided into anterior, inferior and posterolateral thirds, corresponding approximately to the distributions of the left anterior descending, right and left circumflex coronary arteries, respectively.[6–8,12,15] Each patient had ≥2 noncontiguous infarcts involving different coronary artery distributions. The total percent infarct size was quantitated by the method of Ideker et al[6] and Sevilla et al,[12] which involved cutting the LV into 5 to 6 transverse slices of approximately equal thickness. Histologic sections of each slice were obtained, and the amount of infarction was calculated by computer-assisted planimetry.[6–8]

In regions where the infarct was patchy, an estimate of the amount of infarcted myocardium was made to the nearest 25% from the histologic sections. Correction for wall thinning in infarcts aged >1 week was performed, because it was possible that this may have been due to loss of necrotic tissue by phagocytosis and scar contraction.[16] The average thickness of the wall in those portions of the slice that were free of fibrosis was used to estimate the original location of the endocardial border of the thinned fibrotic portion.

Electrocardiographic techniques: All available electrocardiograms obtained after the final infarct were reviewed, and the one closest to death that met the aforementioned inclusion criteria was selected. Infarct size was estimated using 54 weighted criteria based on quantitative QRS abnormalities on 10 leads (I, II, aVL, aVF and V_1–V_6). Manual application of this system has been described previously.[11]

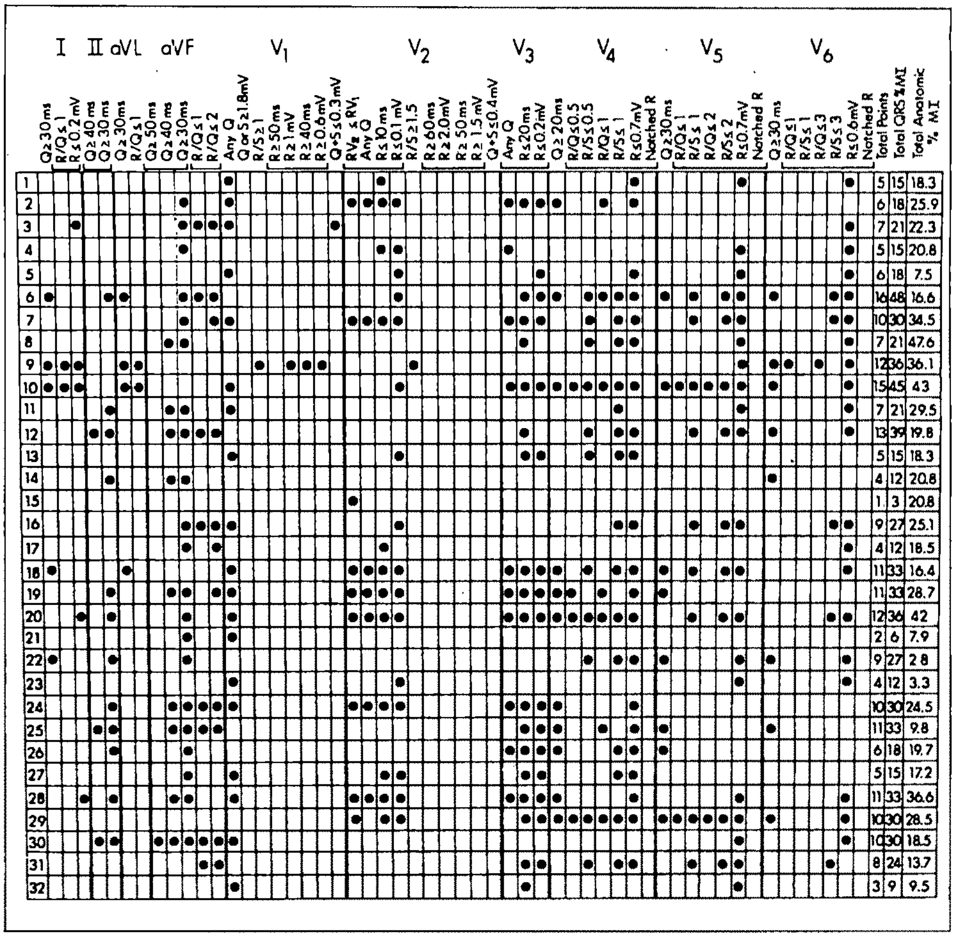
Figure 2 shows the QRS scoring system, which consists of 54 criteria, and the points assigned to each criterion. The maximum number of points (QRS score) that can be accumulated is 32. Percent infarction is estimated by multiplying QRS score by 3, yielding a total of 96%, because each point represents 3% infarction of the LV.[11] The total anatomic percent infarction was then

Complete 54-Criteria/32-Point QRS Scoring System

Lead	Max Lead Points	Criteria	Pts
I	(2)	$Q \geq 30$ ms	(1)
		$R/Q \leq 1$	(1)
		$R \leq 0.2$ mV*	(1)
II	(2)	$Q \geq 40$ ms	(2)
		$Q \geq 30$ ms	(1)
aVL	(2)	$Q \geq 30$ ms	(1)
		$R/Q \leq 1$	(1)
aVF	(5)	$Q \geq 50$ ms	(3)
		$Q \geq 40$ ms	(2)
		$Q \geq 30$ ms	(1)
		$R/Q \leq 1$	(2)
		$R/Q \leq 2$	(1)
V_1	(2)	Any Q	(1)
		Q or $S \geq 1.8$ mV*	(1)
	(4)	$R/S \geq 1$	(1)
		$R \geq 50$ ms	(2)
		$R \geq 1.0$ mV*	(2)
		$R \geq 40$ ms	(1)
		$R \geq 0.6$ mV*	(1)
		Q and $S \leq 0.3$ mV*	(1)
V_2	(1)	Any Q	(1)
		$R \leq 10$ ms	(1)
		$R \leq 0.1$ mV*	(1)
		$R \leq R\,V_1$ mV*	(1)
	(4)	$R/S \geq 1.5$	(1)
		$R \geq 60$ ms	(2)
		$R \geq 2.0$ mV*	(2)
		$R \geq 50$ ms	(1)
		$R \geq 1.5$ mV*	(1)
		Q and $S \leq 0.4$ mV*	(1)
V_3	(1)	Any Q	(1)
		$R \leq 20$ ms	(1)
		$R \leq 0.2$ mV*	(1)
V_4	(3)	$Q \geq 20$ ms	(1)
		$R/S \leq 0.5$	(2)
		$R/Q \leq 0.5$	(2)
		$R/S \leq 1$	(1)
		$R/Q \leq 1$	(1)
		$R \leq 0.7$ mV*	(1)
		Notched R*	(1)
V_5	(3)	$Q \geq 30$ ms	(1)
		$R/S \leq 1$	(2)
		$R/Q \leq 1$	(2)
		$R/S \leq 2$	(1)
		$R/Q \leq 2$	(1)
		$R \leq 0.7$ mV*	(1)
		Notched R*	(1)
V_6	(3)	$Q \geq 30$ ms	(1)
		$R/S \leq 1$	(2)
		$R/Q \leq 1$	(2)
		$R/S \leq 3$	(1)
		$R/Q \leq 3$	(1)
		$R \leq 0.6$ mV*	(1)
		Notched R*	(1)

* New criterion. Max = maximal.

FIGURE 2. When >1 criterion is met, one with most points is selected. "Notched R" means reversal in waveform direction that begins within first 40 ms of QRS onset. (Reproduced from Hindman et al[11] with permission of publisher.)


I
II
aVL
aVF
V1
V2
V3
V4
V5
V6
Q≥30ms
R/Q≤1
R≤0.2mV
Q≥40ms
Q≥30ms
Q≥30ms
R/Q≤1
Q≥50ms
Q≥40ms
Q≥30ms
R/Q≤1
R/Q≤2
Any Q
Q or S≥1.8mV
R/S≥1
R≥50ms
R≥1mV
R≥40ms
R≥0.6mV
Q+S≤0.3mV
RV2 ≤RV1
Any Q
R≤10ms
R≤0.1mV
R/S≥1.5
R≥60ms
R≥2.0mV
R≥50ms
R≥1.5mV
Q+S≤0.4mV
Any Q
R≤20ms
R≤0.2mV
Q≥20ms
R/Q≤0.5
R/S≤0.5
R/Q≤1
R/S≤1
R≤0.7mV
Notched R
Q≥30ms
R/Q≤1
R/S≤1
R/Q≤2
R/S≤2
R≤0.7mV
Notched R
Q≥30 ms
R/Q≤1
R/S≤1
R/Q≤3
R/S≤3
R≤0.6mV
Notched R
Total Points
Total QRS % MI
Total Anatomic % MI

	Total Points	Total QRS % MI	Total Anatomic % MI
1	5	15	18.3
2	6	18	25.9
3	7	21	22.3
4	5	15	20.8
5	6	18	7.5
6	16	48	16.6
7	10	30	34.5
8	7	21	47.6
9	12	36	36.1
10	15	45	43
11	7	21	29.5
12	13	39	19.8
13	5	15	18.3
14	4	12	20.8
15	1	3	20.8
16	9	27	25.1
17	4	12	18.5
18	11	33	16.4
19	11	33	28.7
20	12	36	42
21	2	6	7.9
22	9	27	2 8
23	4	12	3.3
24	10	30	24.5
25	11	33	9.8
26	6	18	19.7
27	5	15	17.2
28	11	33	36.6
29	10	30	28.5
30	10	30	18.5
31	8	24	13.7
32	3	9	9.5

FIGURE 3. QRS point scores for each of 32 patients. MI = myocardial infarction.

correlated with that estimated by the complete Selvester QRS scoring system. Finally, the sensitivity of each criterion in identifying the presence of ≥2 infarcts was evaluated.

Statistical analysis: A Spearman correlation was used to determine the relation between total anatomic and QRS-estimated infarct size.

RESULTS

Mean heart weight was 458 g (range 197 to 752). Twenty-four patients had significant (≥75%) reduction in cross-sectional areas of all 3 major coronary arteries, 2 had significant involvement of the left anterior and right coronary arteries only, and 1 had significant narrowing of the left anterior descending alone. Quantitative anatomic analysis of the coronary obstructive lesions was not available in the remaining 5 patients.

Figure 3 indicates all QRS scoring criteria satisfied for each of the 32 patients. The total electrocardiographic and anatomic infarct sizes are also indicated for each patient. Mean total infarct size determined anatomically was 23% (range 3 to 48), and mean infarct size estimated by the electrocardiogram was 24% (range 3 to 48).

Figure 4 shows the relation between infarct size determined anatomically and that estimated by electrocardiogram. The coefficient of correlation was 0.44 (p = 0.01). Anatomic size was underestimated by ≥15% in 2 patients, and overestimated by that amount in 4.

Table I lists all 54 criteria in the Selvester scoring system, and the incidence (in decreasing order) in which each was met. The inferior myocardial infarction criterion of Q ≥30 ms in aVF was most frequently met, followed by the decreased R amplitude in V_4–V_6 representing apical involvement. Anterior myocardial infarc-

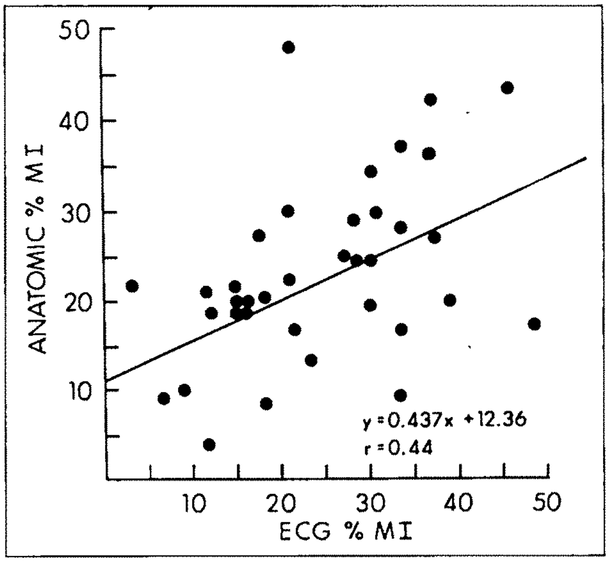


FIGURE 4. Correlation between anatomically estimated infarct size and that estimated by QRS scoring system. ECG = electrocardiographic; MI = myocardial infarction.

TABLE I Incidences (in decreasing order) in Which the Criteria Were Met

Lead	Criteria	Incidence (%)	Lead	Criteria	Incidence (%)
aVF	Q ≥30 ms	66	II	Q ≥40 ms	9
V_4	R ≤0.07	63	I	R/Q ≤1	6
V_5	R ≤0.07	63	aVL	R/Q ≤1	6
V_6	R ≤0.06	63	V_5	R/Q ≤1	6
V_1	Any Q	59	V_5	R/Q ≤2	6
V_2	R ≤0.1 mV	50	aVF	Q ≥50 ms	3
V_3	R ≤0.2 mV	50	V_1	R/S ≥3	3
V_3	R ≤20 ms	50	V_1	R ≥1.0 mV	3
V_4	R/S ≤1	44	V_1	R ≥40 ms	3
II	Q ≥30 ms	41	V_1	R ≥0.6 mV	3
V_4	Q ≥20 ms	38	V_1	Q and S ≤0.3	3
aVF	R/Q ≤2	38	V_2	R/S ≥1.5	3
V_2	R ≤10 ms	34	V_6	R/Q ≤1	3
V_4	R/S ≤0.5	34	V_6	R/Q ≤3	3
V_3	Any Q	31	V_1	Q or S ≥1.8	0
V_5	R/S ≤1	28	V_1	R ≥50 ms	0
V_5	R/S ≤2	28	V_2	R ≥60 ms	0
aVF	Q ≥40 ms	28	V_2	R ≥2.0 mV	0
aVF	R/Q ≤1	28	V_2	R ≥50 ms	0
V_2	$RV_2 \leq RV_1$	25	V_2	R ≥1.5 mV	0
V_6	Q ≥30 ms	25	V_2	Q and S ≤0.4 mV	0
V_2	Any Q	22	V_6	R/S ≥1	0
V_4	R/Q ≤1	22	V_4	Notched R	0
V_5	Q ≥30 ms	22	V_5	Notched R	0
I	Q ≥30 ms	16	V_6	Notched R	0
I	R ≤0.2 mV	16	V_2	R ≥60 ms	0
aVL	Q ≥30 ms	13	V_2	R ≥2.0 mV	0
V_4	R/Q ≤0.5	13	V_2	R ≥50 ms	0
V_6	R/S ≤3	13			

tion criteria in V_1, V_2 and V_3 had 59, 50 and 50% frequencies, respectively. The 12 criteria in V_1 and V_2 relating to the posterior location were either never met or present in only 1 patient.

DISCUSSION

Even though all patients in this study had >1 infarct, the total anatomic sizes remained in the same range as that previously reported for those with single infarcts.[6-8,12] However, QRS-estimated sizes were larger. Only 7 of 71 (10%) patients with single infarcts had QRS-estimated size >30% vs 10 of 32 (31%) patients with multiple infarcts.

There was a lower correlation between QRS-estimated and anatomically documented sizes of multiple infarcts (r = 0.44) than of single infarcts in anterior (r = 0.91), inferior (r = 0.60) or posterolateral (r = 0.70) locations.[6-8] However, cancellation of QRS criteria by infarcts in the opposing wall does not appear to be a major factor, because only 2 patients had as much as 15% underestimation of anatomic size. Conversely, there were 4 patients with anatomic sizes ranging between 9 and 20%, but QRS-estimated sizes between 30 and 50%. This result was unexpected, and no explanation is readily apparent. A previous study[16] demonstrated that fibrotic infarcts are more often overestimated with electrocardiography, and that may have had an important effect in this study because of the prolonged time between the first infarct and death.

Though many patients[13] had infarction involving the posterolateral myocardium, only 2 of these achieved QRS points relating to posterior infarct. Six of the 12 criteria in leads V_1 and V_2 for posterior infarction were never met, and no patient met >1 criterion. This result is in marked contrast to that observed in patients with isolated posterolateral infarcts where 10 of the 20 patients (50%) achieved QRS points for the posterior myocardial infarction location.[12] One may assume that cancellation of QRS changes by infarction of the opposing anterior wall of the LV produced falsely negative criteria for posterior involvement.

The criteria of "notched R wave" in V_4, V_5 and V_6 were never satisfied in these 32 patients. Indeed, these criteria were only met in 3 of the 71 patients with single infarcts, and on each occasion, the small R-amplitude criterion was also satisfied. Likewise, the V_1 S ≥1.8 mV criterion was never identified in these patients with multiple infarcts and appeared only 3 times in those with single infarcts. If these results are confirmed by other studies, these 4 criteria can be discarded from future QRS scoring systems.

A study is in progress of this group of 32 patients with multiple infarcts and of the 71 with single infarcts to correlate the anatomic and electrocardiographic results in the various areas of the LV. Selvester et al[17] developed a method for distributing the infarction indicated by each of the 54 criteria into 12 anatomic segments. This analysis will be used to guide revisions in the scoring system.

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Percutaneous Transluminal Coronary Rotary Ablation with Rotablator (European Experience)

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This study reports the results from 3 European centers using rotary ablation with Rotablator™, a device that is inserted into the coronary artery and removes atheroma by grinding it into millions of tiny fragments. Rotary ablation was performed in 129 patients. Primary success (reduction in percent luminal narrowing >20%, residual stenosis <50%, without complications) was achieved by rotary angioplasty alone in 73 patients (57%). An additional 38 patients (29%) had successful adjunctive balloon angioplasty. Thus primary success was achieved in 111 patients (86%) at the end of the procedure. Acute occlusion occurred in 10 patients (7.7%). Recanalization was achieved by balloon angioplasty in 7: urgent bypass grafting was undertaken in 2. Q-wave and non-Q-wave myocardial infarction occurred in 3 and 7 patients, respectively. No deaths occurred. Follow-up angiography was performed in 74 patients (60%). Restenosis, defined as the recurrence of significant luminal narrowing (>50%) occurred in 17 of 37 patients (46%) who underwent rotary ablation alone, and 11 of 37 patients (30%) who had adjunctive balloon angioplasty. The overall angiographic restenosis rate was 37.8%. In conclusion, rotary ablation is technically feasible, and relatively safe in the coronary circulation. The low primary success rate reflects the limited size of the device, which can be introduced through available guiding catheters, and limits the use of rotary ablation as a stand-alone procedure to lesions in small arteries or in distal locations. No reduction in restenosis was seen, but the role of this device combined with balloon angioplasty in larger arteries needs to be further defined.

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The original description of percutaneous transluminal coronary angioplasty has led to major changes in the clinical practice of cardiology, and has stimulated innovative expression in research. In the last 5 years, significant improvements have been made in the initial balloon catheter system described by Gruentzig et al.[1] However, the major problem of restenosis, which occurs in up to 40% of cases after an initially successful procedure,[2] and continuing technical difficulties in dealing with certain types of lesion (particularly those that are calcified or in distal locations) have stimulated research into alternative methods of dealing with atheromatous coronary obstructions. One such technique, coronary atherectomy, has been developed to produce an improvement in lumen diameter by direct mechanical removal of atherosclerotic material from the vessel wall in situ. Several techniques for this purpose have been described including directional (or excisional) atherectomy, transluminal extraction atherectomy, and high speed rotary ablation. In this study, we present the results obtained in 3 European centers using high-speed rotary ablation with Rotablator™.

METHODS

The Rotablator (Heart Technology, Inc., Bellvue, Washington) consists of an abrasive tip (Figure 1) welded to a long flexible drive shaft tracking along a central flexible guidewire. The abrasive tip is an elliptically shaped burr, manufactured in various sizes (from 1.0 mm to 2.75 mm in diameter), whose distal portion is coated with diamond chips 30 to 50 μ in diameter. Rotational energy is transmitted by a disposable compressed air motor that drives the flexible helical shaft at very high speeds (up to 190,000 rpm). The number of revolutions per minute is measured by a fiberoptic light probe and displayed on a control panel. The speed of rotation is controlled by the air pressure, which is itself controlled by the operator using a foot pedal. During rotation, a small volume of sterile saline solution irrigates the catheter sheath to lubricate and cool the rotating parts. The burr and the drive shaft move freely over a central coaxial guide wire (0.009 inch in diameter), with a flexible radioopaque platinum distal part (20 mm long), which does not rotate with the burr during abrasion. This central guidewire can be controlled and moved with a pin vise. The wire and the abrasive tip can be advanced independently, which allows the wire to be placed in a safe distal location before the burr is advanced into the diseased artery.

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Protocol: All patients received nifedipine (60 mg orally in 3 divided doses) and aspirin (500 mg orally) the day before the procedure. Chlorodiazepate (50 mg intravenously) was given on the day of the procedure as premedication. A sheath (9Fr) was inserted into the femoral artery under local anesthesia and a standard 9Fr guiding catheter was advanced to the ostium of the coronary artery. After intracoronary injection of isosorbide dinitrate (2 mg), a baseline angiogram was recorded in 3 projections, and heparin (10,000 IU) was given intravenously.

Rotary ablation began with the placement of the small guidewire across the lesion to a safe distal vessel location, sometimes guided by a 3Fr infusion catheter which was positioned first. The burr and the drive shaft were then manually advanced over the guidewire to the site of the lesion, and rotation was begun. When an adequate speed of rotation (>150,000 rpm) had been achieved, the abrasive tip was advanced gently over the guidewire. If resistance was encountered the tip was successively pulled back and advanced to maintain a high speed of rotation. Several slow passes were usually required to achieve maximal plaque removal. Typical results of the procedure are shown in Figures 2 and 3. The angiographic results of the patients studied in Lille and Rotterdam were assessed by computerized quantitative coronary angiography (as described later). When the residual stenosis after atherectomy remained significant (>50%), an additional percutaneous balloon angioplasty was performed. Patients were discharged with nifedipine (60 mg/day) and aspirin (100 to 500 mg/day) and underwent repeat coronary angiography 3 to 6 months after the procedure. The study protocol was approved by the local Research Ethics Committee, and written informed consent was obtained from all patients.

Primary success of rotary ablation was defined as a significant reduction (>20%) of stenosis with residual stenosis <50% without complications during hospitalization. Restenosis was defined as the recurrence of a significant narrowing (reduction of luminal diameter >50%).

Study population: One hundred twenty-nine patients (107 men and 22 women, mean age 57 ± 8 years, range 33 to 68) underwent rotary ablation. Sixty-five patients were treated in Lille, France, 54 in Mainz, Germany, and 10 in Rotterdam, the Netherlands.

Clinical characteristics: Most of the patients (n = 68 or 53%) had severe (Canadian Cardiovascular Grade 3) stable effort angina, 13 or 10% had angina on effort and at rest, 15 (11.5%) had unstable angina, 15 complained of angina at rest, and only 6 (5%) had atypical chest pain; finally, 12 patients had no chest pain.

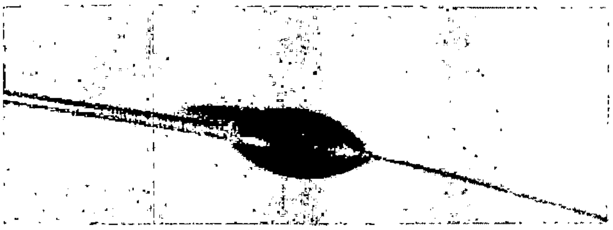

FIGURE 1. Distal part of the Rotablator with the burr.

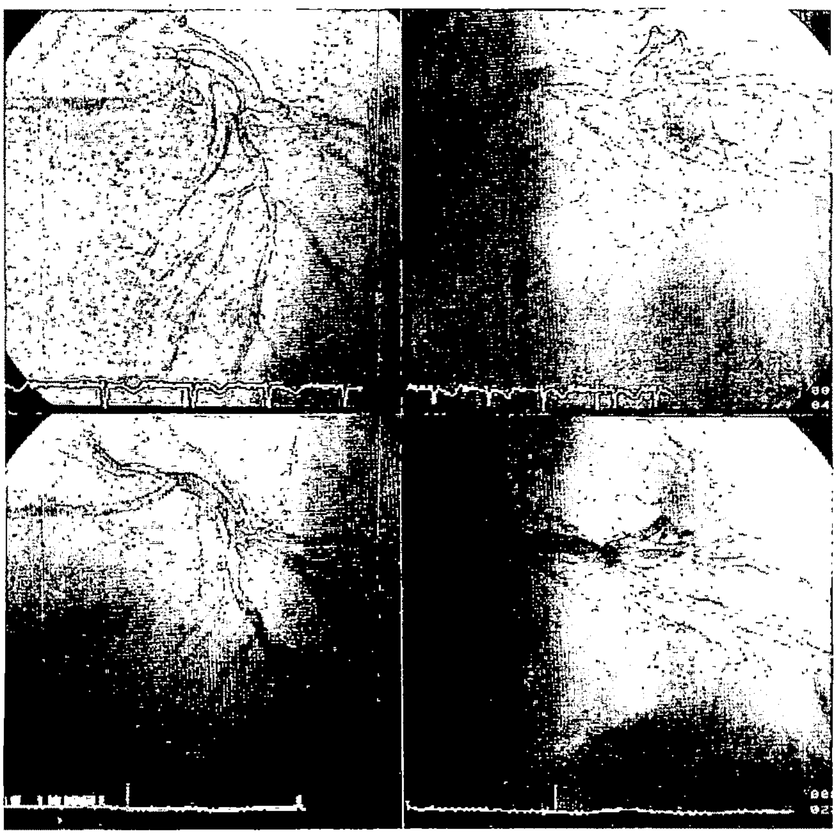

FIGURE 2. Rotablator as a stand-alone procedure for a lesion of the proximal left anterior descending coronary artery. *Upper panels,* before Rotablator; *lower panels,* after Rotablator.

TABLE I Quantitative Coronary Analysis After Rotary Ablation

Ablation	Rotary Ablation Before	Rotary Ablation After	After Rotary + Balloon
Rotary ablation (mm)	0.72 ± 0.30	1.46 ± 0.43	—
Stand alone procedure (%)	73 ± 12	42 ± 13*	—
Rotary ablation + balloon angioplasty			
mm	0.49 ± 0.37	1.14 ± 0.36*	2.2 ± 0.46*
%	80 ± 12	61 ± 13	31 ± 9*

*p <0.01.

Angiographic data: Coronary angiograms showed 1-, 2- and 3-vessel disease in 68, 25 and 7%, respectively. In all patients only 1 coronary segment was treated by rotary ablation. The procedure was performed on the left anterior descending artery in 63 patients, the right coronary artery in 47 patients and the circumflex artery in the remaining 19 patients. Most of the stenoses were routine lesions: According to American Heart Association/American College of Cardiology classification, 48% of the patients had type A lesions; types B and C were observed in 36 and 16% respectively. Twenty-six lesions were calcified.

Quantitative coronary angiography: Coronary arteriograms were analyzed with use of a computerized automatic-analysis system (Computerized Assisted Evaluation of Stenosis and Restenosis). The cine film was projected with a Tagarno projector and the end-diastolic frame selected for analysis was scanned with a CCD JVC video camera. The signal produced by the video camera was digitized and processed with a software system on a 386 computer provided with an automatic edge-detection algorithm. The diameter of the coronary catheter was used to convert the imaging data from pixels to millimeters. The frames for analysis were chosen by a cardiologist who was not involved in the study protocol. The dilated vessel segment was defined by measuring the distance from a side branch of the dilated vessel to the narrowest point of the stenosis on the angiogram immediately before ablation. All measurements were performed on angiograms recorded after the intracoronary injection of 2 mg of isosorbide dinitrate.

Statistical analysis: All data are expressed as mean ± SD. Comparisons between vessel diameters (or percentage reduction in luminal diameter) before rotary ablation, immediately after rotary ablation and at follow-up were performed with use of paired Student's *t* tests. A p value <0.05 was considered statistically significant.

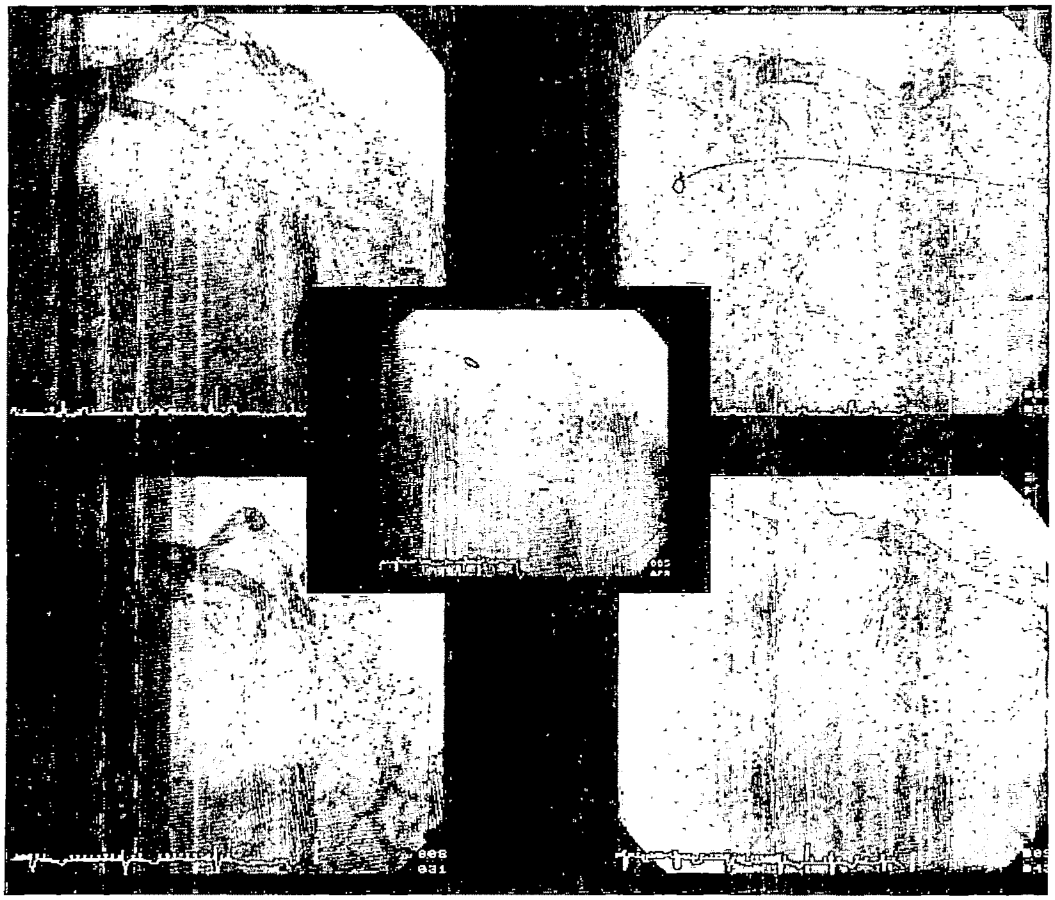

FIGURE 3. Rotary ablation with a 2.5 mm burr of a mid–left anterior descending lesion. *Upper panels,* before Rotablator; *lower panels,* after Rotablator.

RESULTS

Rotary ablation was performed in 128 patients; in 1 patient the guidewire could not be passed across a very tight and tortuous stenosis. Rotary ablation as a stand-alone procedure was achieved in 88 patients; in 40 patients, rotary ablation was completed by adjunctive balloon angioplasty because of abrupt closure in 10 and insufficient results in 30 who still had significant stenosis after the procedure. Thus, primary success was achieved by rotary ablation alone in 73 patients (57%). This relatively low success rate was mainly the result of the small size of the channel created by rotary ablation. This was due to the limited size of the burr acceptable for guiding catheters available at the beginning. With the help of additional successful balloon angioplasty in 40 patients the overall success rate of 86% (111 of 129 patients) was at the end of the procedure.

Complications: A transient (few seconds) bradycardia was observed early in our experience in 6 patients. In 3 patients this occurred during a procedure on the right coronary artery and may have been related to microembolization of the atrioventricular nodal artery. In all subsequent treatment of the right coronary artery a pacing catheter was placed in the right ventricle before the procedure. Immediately after the procedure 8 patients developed a long diffuse coronary spasm distal to the treated site, which was promptly relieved by the intracoronary injection of isosorbide dinitrate. Abrupt closure occurred during the procedure in 10 patients (7.8%): In 7, the lesion was easily recrossed with a balloon, 2 required rapid bypass surgery without further complications or infarction, and in 1 recanalization of the abrupt closure was not attempted because the area supplied by the vessel was relatively small (no increase in cardiac enzymes and no subsequent complications occurred in this particular patient). Three patients developed late occlusion (at 6 hours, 24 hours and 6 days after the procedure). Myocardial infarction (Q wave in 3, non-Q-wave in 7) developed in 10 patients (7.8%). Except for these 10 patients, serial creatine kinase measurements never exceeded the upper normal limit. There were no deaths related to the procedure.

Quantitative angiographic measurements: Before and immediately after rotary ablation, quantitative angiographic measurements (as previously outlined) were performed in the patients studied in Lille and Rotterdam (n = 69). The results of rotary ablation as a stand-alone procedure are outlined in Table I. The mean minimal lumen diameter increased from 0.72 ± 0.30 mm before to 1.46 ± 0.43 mm immediately after the procedure ($p < 0.001$). The ratio minimal luminal diameter/burr size was 0.7 ± 0.25. The mean percent reduction in internal luminal diameter decreased from 73 ± 12 to 42 ± 13%. Where the procedure was completed by adjunctive balloon angioplasty the mean residual minimal diameter was 2.2 ± 0.46 mm, and the mean residual percent stenosis was 31 ± 9%.

Angiographic follow-up: Seventy-four patients underwent repeat coronary angiography at a mean of 4.6 months (range 3 to 6) after the procedure. The angiographic results at follow-up were analyzed in 2 groups of patients: group A (n = 37) underwent rotary ablation as a stand-alone procedure and group B (n = 37) underwent rotary ablation with adjunctive balloon angioplasty. Seventeen patients (46%) in group A had typical restenosis. In group B, restenosis was observed in 29.7% of patients. For the whole group the restenosis rate was 37.8%.

DISCUSSION

The main mechanism of action of Rotablator is an abrasion of the occlusive material allowing restoration of lumen patency. The diamond chips on the burr remove material in millions of tiny particles. Previous experimental studies in animals, and observations made on segments of human iliac arteries treated with rotary angioplasty showed that the resulting arterial lumen was smooth and polished.

Two major concerns have been expressed regarding the use of rotary ablation in the coronary circulation; one relates to its potential to damage adjacent nonatheromatous tissue, the other to the size of the particles generated by the procedure. Studies in animals and in human peripheral arteries[3–7] have shown that rotary ablation selectively removes firmer noncompliant material, while the normal elastic tissue is deflected away from the probe. This potential for selective removal of diseased tissue, with particular affinity for harder material such as calcium, is obviously of great clinical relevance. The removal of the endothelium may contribute to the occurrence of vasospasm which we observed in some patients. However, in our patients vasospasm was usually seen 2 or 3 cm beyond the site of ablation and may have been related to vibrations transmitted to the guidewire during rotation of the burr. A similar phenomenon has been reported by Hansen[5] after rotational atherectomy in a rabbit model of atheroma.

No-flow phenomenon, transient bradycardia and atrioventricular blocks may be related to production of microcavitations. As a result of high velocity at the burr, surface cavitations are produced according the Bernoulli equation, and this was previously documented in experimental studies.[8]

The second concern relates to the size of particles created by rotary ablation. This concern has been investigated in several animal models[6] and in human peripheral arteries. These observations suggest that the debris generated by rotary ablation is usually small enough to pass safely through the capillary bed. Moreover, in 32 cases we assessed left ventricular motion before and after rotary ablation and we did not observe wall motion abnormality after rotary ablation.

The size of the burr used in the coronary artery is a limitation of the Rotablator. The device must be inserted in the coronary artery through a guiding catheter. However, even with the largest available guiding catheters, the inside luminal diameter does not exceed 2.5 mm. Thus, although burrs are available in sizes up to 4.5 mm, only those <2.5 mm in diameter can be used in the coronary circulation. Moreover, the ratio residual minimal lumen diameter/burr diameter is only 0.7: this suggests that the "effective abrasive diameter" is inferior to the maximal diameter of the burr. It is very likely that at the end of abrasion, the elastic arterial wall deflects away, allowing the passage of the device through the lesion. From these experimental observations and our early clinical experience 2 different strategies may be adopted. One approach would be to start with an intentionally undersized burr, with stepwise increments in size until an optimal result is obtained. The other would involve the use of a small burr to "debulk" the vessel, leaving a smooth residual surface, and to complete the procedure with conventional balloon angioplasty but using a very low inflation pressure. The results in our patients would support this second approach. Until further information from comparative studies and longer follow up data are available, the role of rotary ablation in the treatment of coronary disease remains to be defined. The available evidence suggests that high-speed rotary ablation appears to be most useful for (1) lesions in vessels of 2.2 to 2.8 mm in diameter, (2) lesions in distal locations, (3) calcified or nondistensible lesions, and (4) eccentric lesions. However, its use should be avoided in patients with (1) lesions in large coronary vessels (>3.7 mm), (2) lesions in vessels with angiographically apparent thrombus, and (3) lesions in degenerated saphenous vein grafts where the atherosclerotic material is likely to be friable.

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Quantitative Angiographic Follow-Up of the Coronary Wallstent in Native Vessels and Bypass Grafts (European Experience — March 1986 to March 1990)

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The coronary stent has been investigated as an adjunct to percutaneous transluminal coronary angioplasty to obviate the problems of early occlusion and late restenosis. From March 1986 to March 1990, 265 patients (308 lesions) were implanted with the coronary Wallstent® in 6 European centers. For this study, the patients were analyzed according to date of implantation (group 1, March 1986 to January 1988; group 2, February 1988 to March 1990) and vessel type (native arteries versus bypass grafts). Quantitative angiographic follow-up was performed in 82% of the study patients. The early in-hospital occlusion rate in the overall group was 15%. Group 1 patients had a 20% rate in contrast to 12% rate in group 2 (p = not significant [NS]). The early occlusion rate in native vessels and bypass grafts was 19 and 8%, respectively (p = 0.019). Restenosis was determined by 2 criteria (criterion 1, ≥0.72 mm loss in minimal luminal diameter from poststent to follow-up; criterion 2, ≥50% diameter stenosis at follow-up) within the stent and in the segments immediately proximal and distal to the stent. The restenosis rate with criterion 1 was 43% in the overall group of patients, 35% in group 1 versus 49% in group 2 (p = NS), and 34% in native vessels versus 54% in bypass grafts (p = 0.016). The second criterion was met by 27% of patients in the overall group, 21% in group 1 versus 32% in group 2 (p = NS), and 18% in native vessel versus 39% in bypass grafts (p = 0.005). The overall mortality during the study period was 6.6% in native arteries and 9% in bypass grafts (6 and 7.9% at 1 year, respectively). The actuarial event-free survival (freedom from death, myocardial infarction, bypass surgery or angioplasty) for native artery patients was 46% at 40 months and for bypass graft patients 37% at 20 months.

It is concluded that early in-hospital occlusions remain a major problem with this device despite improvement in the later experience. Although patients with bypass grafts had a significantly lower early occlusion rate than those with implantation of native arteries, a significantly higher rate of late restenosis limited the early benefits of stenting. The indications for stenting remain unknown and require results of randomized clinical studies.

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In 1986, the first coronary Wallstent™ implantation ushered in a new era in interventional cardiology with the purpose of circumventing the 2 major limitations of coronary angioplasty, early acute occlusion and late restenosis.[1] As with all new procedures, operators of the device had to struggle with their own learning curves at the same time that anticoagulation regimens and clinical indications and contraindications evolved from their clinical experience. In May 1988, the 5 European centers testing this device agreed to set up a core laboratory for quantitative angiographic analysis in Rotterdam to assess the results objectively. In a previous publication from our group, the late angiographic and clinical follow-up of the initial 105 patients was reported.[2] These stent implantations were predominantly performed in native coronary vessels. In the period from February 1988 until March 1990, an additional 160 patients underwent stent implantation in the coronary circulation. This second group was characterized by a predominance of bypass vessels and a different set of indications. In this report, we compared the late quantitative angiographic and clinical follow-up of this second group of patients with the initial group, and assessed bypass grafts versus native vessels. In particular, we

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TABLE I Stent Implantations According to Date of Implantation

	Group 1 (March 1986–January 1988)	Group 2 (February 1988–March 1990)
Vessels	107	175
Stents/narrowings	117/114	266/194
Site of narrowings		
Bypass conduits	29 (18%)	116 (60%)
Native vessels	94 (82%)	78 (40%)
LAD	62 (54%)	29 (15%)
LC	8 (7%)	10 (5%)
Right	24 (21%)	39 (20%)

LAD = left anterior descending artery; LC = left circumflex artery.

were interested in determining whether the changing patterns of patient selection and management based on the initial experience resulted in improved rates of early occlusion and late restenosis and whether the results of stents implanted in bypass grafts differed from native vessels.

METHODS

Study patients: Two hundred sixty-five patients (308 narrowings) were enrolled after obtaining informed consent between March 1986 and March 1990 at the participating centers. The study protocol was approved by the individual hospital ethics committees. The mean age of the population was 58 ± 11 years and 84% were men. The study patients were grouped according to the date of implantation (March 1986 to January 1988, February 1988 to March 1990, groups 1 and 2, respectively) and the vessel type (native vessel versus bypass graft) (Table I). The first period of stent implantations, until January 1988, has previously been reported.[2] Almost 90% of the first group underwent implantation at either Lausanne (n = 56) or Toulouse (n = 32). However, in the second period, about 80% of the patients underwent implantation in Rotterdam (n = 80) and in Lausanne (n = 43). In Group 1, 117 stents were implanted in 114 narrowings, of which 82% were in native vessels (in particular the left anterior descending artery). In group 2, 266 stents were implanted in 194 narrowings, predominantly in bypass grafts. In this group, the right coronary artery was the most common vessel implanted in the native circulation. Two patients had stents placed in both a bypass graft and a native vessel. The indications for stenting also differed between the 2 vessel types (Figure 1). Native vessels were primarily stented to prevent a second restenosis or as a bail-out procedure for angioplasties complicated by abrupt closure or large dissections that interrupted anterograde flow and were associated with clinical and electrocardiographic signs of ischemia. However, in bypass grafts, the principle indication was for primary lesions that had not been previously treated with angioplasty.

In this trial, the endovascular prosthesis, Wallstent®, was provided by Schneider Europe, Zurich. The method of implantation and description of this stent has previously been reported.[1–5] Unconstrained stent diameter ranged from 2.5 to 6 mm and was selected to be 0.50 mm larger than the stented vessel. In an effort to alleviate the problem of acute thrombosis, the stent design was changed in April 1989 with the introduction of a polymer-coated stent (Biogold®) for some stent sizes. By August 1989, all manufactured stents contained this particular polymer coating.

The anticoagulation for the first period of implantation has previously been described.[2] Based on this initial clinical experience, a uniform anticoagulation schedule was followed at the centers. Therapy with acetylsalicylic acid, 1 g orally, was begun 1 day before the procedure. At the beginning of the procedure, patients received heparin, 10,000 IU intravenously, and in some cases, dextran infusions (500 mg/4 hours) were also given. Heparin (10,000 IU) and urokinase (100,000 U) were administered by intracoronary infusion during the procedure. After the procedure, the heparin infusion was adjusted according to the activated partial thromboplastin time (desired range 80 to 120 seconds) in addition to initiating oral vitamin K antagonist therapy. Heparin was discontinued after the therapeutic oral anticoagulation level was stabilized (international normalized ratio >2.3). Acetylsalicylic acid (100 mg/day), dipyridamole (300 to 450 mg/day), and in some patients sulfinpyrazone (400 mg/day) were also administered.

Quantitative coronary arteriography and restenosis criteria: All cineangiograms were analyzed at the core laboratory in Rotterdam using the computer-assisted cardiovascular angiography analysis system which has previously been discussed in detail.[6,7] The minimal luminal diameter and percent diameter stenosis were determined before and after angioplasty, immediately after stent implantation and at long-term follow-up in all patients using the average of multiple matched views with orthogonal projections wherever possible. The min-

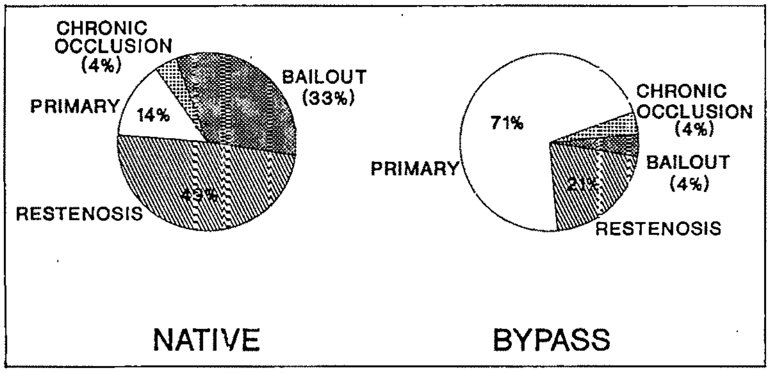

FIGURE 1. The indications for stenting in native arteries and bypass grafts. Primary = primary atherosclerotic lesion that has not been previously treated by angioplasty or stenting.

imal luminal diameter (and the diameter stenosis using the reference diameter of the segment) of each segment immediately proximal and distal to the stent was also measured.

Two different sets of criteria were applied to determine the restenosis rate. We have found a change in minimal luminal diameter of ≥0.72 mm (criterion 1) to be a reliable indicator of angiographic progression of vessel narrowing and by no means implies functional or clinical significance.[3,4,8] This value takes into account the limitations of coronary angiographic measurements and represents 2 times the long-term variability (i.e., the 95% confidence intervals) for repeat measurements of a coronary obstruction using our system. Criterion 2 for restenosis was an increase of the diameter stenosis from <50% after stent implantation to ≥50% at follow-up. This criterion was selected since common clinical practice continues to assess lesion severity by a percent stenosis. The 2 criteria were assessed within and in the segment immediately adjacent (proximal and distal) to the stent.

In this study, late (i.e., documented after the initial discharge from hospital) occlusion ($n = 10$ patients, 16 lesions) was regarded as restenosis. This contrasts with our earlier report in which we calculated a total occlusion rate that was then separated into early (in hospital) and late occlusions.[2] In that report, the early and late occlusions were analyzed separately from the restenotic lesions. The current change was initiated to be consistent with our reports of late follow-up of angioplasty.[4,9]

Statistical methods: The data obtained by quantitative angiographic analysis are given as mean ± standard error of the mean. The means for each angiographic variable before angioplasty, after stent and at follow-up were compared by analysis of variance. If significant differences were found, 2-tailed t tests were applied to pairs of data. The occlusion and restenosis rates were compared using a chi-square test. A statistical probability <0.05 was considered significant.

The late clinical follow-up was determined according to a life-table format using the Kaplan-Meier method.[10] The following events were considered clinical end points: death, myocardial infarction, bypass surgery or nonsurgical revascularization (angioplasty or atherectomy). The life table was constructed according to the initial clinical event.

RESULTS

The angiographic follow-up for the entire study population was 82% (Table II). This includes patients with documented early occlusions during hospital admission ($n = 40$) in addition to patients who had late (after the initial hospital discharge) angiography. The reasons why follow-up angiography could not be performed are listed in Table II. The time to angiographic follow-up was 6.6 ± 4.8 months if early occlusions are excluded and 5.7 ± 5.0 months with the early occlusions.

The angiographic data for individual lesions in bypass grafts and native vessels are presented in Figures 2 and 3. In native vessels, there was a mean increase in minimal luminal diameter (mm) from 1.17 ± 0.04 to 2.53 ± 0.04 immediately after stenting ($p < 0.0001$), but a late deterioration to 1.99 ± 0.07 ($p < 0.0001$ versus the poststent result) if early occlusions are excluded and 1.59 ± 0.09 with the inclusion of the early occlusions ($p < 0.0001$). Similarly, the minimal luminal diameter increased significantly in bypass narrowings from 1.39 ± 0.06 to 2.81 ± 0.06 after stenting with a late reduction to 2.21 ± 0.11 and 2.03 ± 0.12 with the exclusion and inclusion of early occlusions, respectively ($p < 0.0001$). Diameter stenosis was significantly re-

TABLE II Angiographic Follow-Up

Implantations (lesions/patients)	308/265	
Early occlusions	41/40	
Late follow-up	214/176	
Total	255/216	(82%)
No angiographic follow-up	53/49	(18%)
Death	10	(4%)
Early bypass surgery	11	(4%)
Refusal	25	(9%)
Technical	3	(1%)
Time to angiographic follow-up		
Excluding early occlusions	6.6 ± 4.8	
Including early occlusions	5.7 ± 5.0	

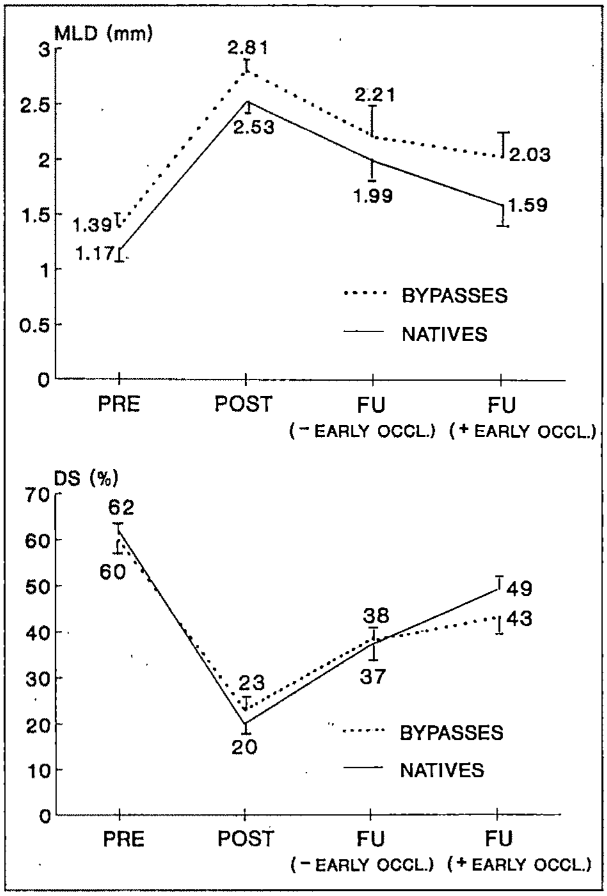

FIGURE 2. ***Top,*** **minimal luminal diameter (MLD) of native vessels and bypass grafts before (PRE) procedure, after (POST) stenting, and at follow-up (FU). Mean values at follow-up have been calculated with and without the inclusion of the early in-hospital occlusions (OCCL.). DS = diameter stenosis.** ***Bottom,*** **percent diameter stenosis (DS) of native vessels and bypass grafts before procedure, after stenting, and at follow-up. Mean values at follow-up have been calculated with and without the inclusion of the early in-hospital occlusions. MLD = minimal luminal diameter.**

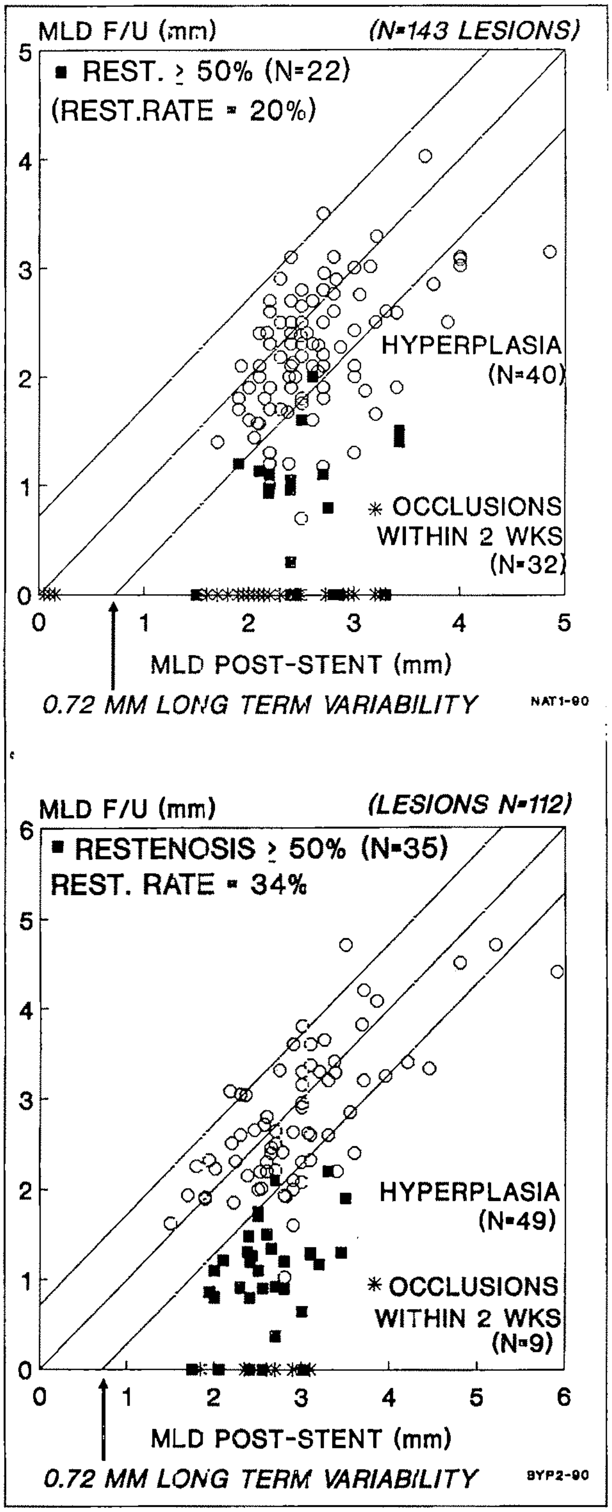

FIGURE 3. Change in the minimal luminal diameter (MLD) for individual lesions in native vessels *(top)* and in bypass grafts *(bottom)* between stent implantation and angiographic follow-up (F/U). The diameter of each segment immediately after implantation is plotted against the diameter at follow-up. The *lines* on each side of the *identity line (diagonal)* represent the limits of long-term variability of repeat measurements (a change of ≥0.72 mm *[arrow]*). All symbols *below the right-hand line* represent stents with involvement of angiographic detectable hyperplasia. *Filled squares* represent lesions with follow-up diameter stenosis ≥50%. Occlusions are located along the x axis, and those that occurred within the first 2 weeks are marked by an *asterisk*. REST. = restenosis.

duced immediately after stenting in bypass grafts from 60 ± 1 to 23 ± 1%, but increased at late follow-up to 43 ± 3 and 38 ± 3% with and without the early occlusions, respectively (p <0.0001 versus the poststent result). Similar changes were observed in native vessels.

In the overall group, the incidence of early in-hospital occlusion was 15% in patients and 13% in lesion. In bypass grafts, early occlusions were documented in 7% of lesions (8% of patients) versus 18% of lesions (19% of patients) in native vessels (in lesions, p = 0.005; in patients, p = 0.016). Three of these native vessel occlusions occurred during the procedure and could not be recanalized. The remaining occlusions presented clinically as acute ischemic syndromes after a successful stenting procedure. Early occlusions were less frequent in group 2 (12%) than in group 1 (20%) patients but not statistically significant. Restenosis in the overall group according to criteria 1 and 2 was 42% and 27%, respectively (Table III). Restenosis according to either definition was significantly higher in bypass grafts (criterion 1, 54%; criterion 2, 39%) than in native vessels (34 and 18%, respectively) (criterion 1, p = 0.016; criterion 2, p = 0.001). Although the restenosis rates by either criterion were higher in group 2 than group 1, these differences were not statistically significant.

The overall mortality during the study period was 9% (n = 9) for bypass grafts and 6.6% (n = 11) for native vessels (8 and 6% at 1 year, respectively). The 1-year mortality rate in group 1 and 2 patients was 7.6 and 7.5%, respectively. In patients who underwent bypass surgery, 4 deaths occurred during the initial hospitalization (2 intracerebral hematomas related to the anticoagulation and 2 myocardial infarctions due to stent occlusion). Two of the 5 late deaths were sudden (at 2 and 18 months), 2 were unrelated to the stent (chronic heart failure, renal failure), and the other death occurred after bypass surgery. In the stented native vessel group, 7 of the 11 deaths occurred in the hospital. These were due to myocardial infarctions resulting from stent occlusion, with the exception of 1 patient with intracerebral bleeding and 1 in cardiogenic shock who underwent stent implantation 24 hours after a myocardial infarction. Two of the 4 late deaths were sudden (at 1.5 and 19 months), 1 was noncardiac (pneumonia) and the other occurred after bypass surgery. The actuarial event-free survival (freedom from death, myocardial infarction, bypass surgery or angioplasty) for native artery patients was 46% at 40 months and for bypass graft patients 37% at 20 months (Figure 4).

DISCUSSION

The coronary Wallstent was initially introduced as an endovascular device to prevent the late restenosis process that limits percutaneous transluminal coronary angioplasty. The indications for and management of patients implanted with this particular prosthesis have evolved as experience and knowledge have increased. In this study, an attempt has been made to separate 2 important factors in the late outcome of patients with stent implantations. The first division, according to date of implantation, provides the clearest picture of the changes in stent applications based on the early experience. Investigators originally believed that the stent could be safely implanted in native vessels and that the benefit of stents would be most apparent in lesions that had already restenosed on at least 1 occasion. However, a high in-hospital occlusion rate was noted, particularly in patients with unstable syndromes, evolving myocardial infarction or angiographic evidence of thrombus. These occlusions, often with disastrous clinical sequelae, convinced most of the investigators that native vessels in general and particularly in the left anterior descending artery (due to the large territory at risk) should only be implanted in bailout situations. Group 2 mainly consisted of patients with bypass grafts who underwent stent implantation for primary lesions and those in whom native vessels were implanted as part of a bailout strategy

TABLE III Late Angiographic Follow-Up: Restenosis Within and Immediately Adjacent to the Stent

	Total	Group 1	Group 2	Native Vessels	Bypass Grafts
Narrowings/patients	214/176	85/75	129/101	111/104	103/74
0.72 mm criterion					
Within stent	75/61	25/21	50/40	35/30	40/31
Adjacent to stent	14/14	5/5	9/9	5/5	9/9
Total	89/75 (42%/43%)	30/26 (37%/35%)	59/49 (46%/49%)	40/35 (36%/34%)	49/40 (48%/54%)
50% diameter stenosis criterion					
Within stent	51/42	17/15	34/27	21/18	30/24
Adjacent to stent	6/6	1/1	5/5	1/1	5/5
Total	57/48 (27%/27%)	18/16 (22%/21%)	39/32 (30%/32%)	22/19 (20%/18%)	35/29 (34%/39%)

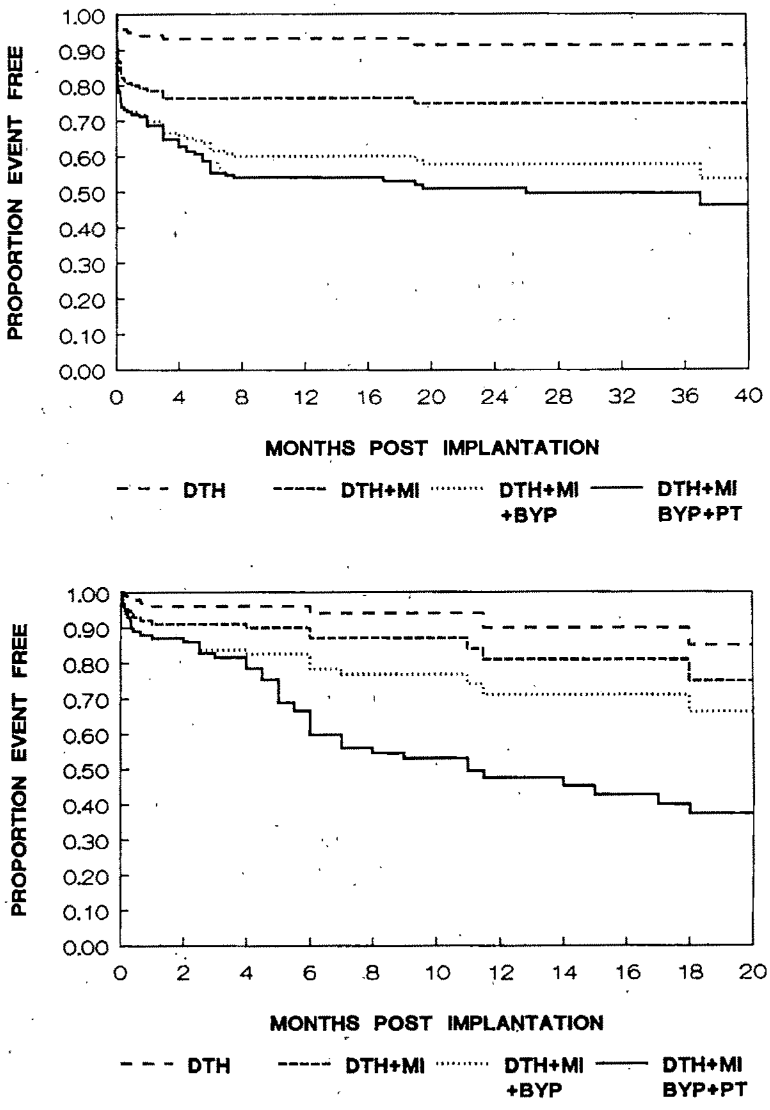

FIGURE 4. Clinical follow-up in native vessels up to 40 months *(top)* and bypass grafts up to 20 months *(bottom)* according to actuarial event-free survival. The y axis represents the proportion of patients without a clinical event, and time after implantation (in months) is along the x axis. The *curves (from upper to lower)* represent freedom from death (DTH) alone; death plus myocardial infarction (MI); death, myocardial infarction plus bypass surgery (BYP); and death, myocardial infarction, bypass surgery plus angioplasty or atherectomy (PT).

after complicated angioplasty. Bypass grafts, in particular, were selected for stent implantations owing to an extremely high rate of restenosis after angioplasty alone, and the larger diameter of these grafts seemed less likely to thrombose than smaller caliber native arterial vessels.[11-14] Bypass lesions, which composed most of the lesions implanted in group 2, were generally more complex than group 1 lesions owing to the advanced age and diffuse nature of the disease in the bypass grafts. As a result, more stents per lesion (1.4 versus 1.1 in native vessels) were required to cover these lesions. Therefore, the significantly lower rate of in-hospital occlusion in patients with bypass grafts versus patients with native vessels (8 versus 19%) and the trend in group 2 versus group 1 (12 versus 20%) are indicative of several possible factors including improvements in anticoagulation regimens, operator experience or larger caliber vessels despite more complex case selection. Higher restenosis rates by both criteria were demonstrated in bypass grafts and in group 2 patients. There are 2 possible explanations for this increase. First, bypass grafts, which are overrepresented in group 2, are known to have higher restenosis rates than native vessels.[11-13] Second, higher restenosis rates may be the "price" for lower occlusion rates. Organization of thrombus at the site of intimal damage may be an important cause of late restenosis after stenting. Although it is often difficult to histologically differentiate thrombus organization from intimal hyperplasia, we have observed an extremely disorganized pattern of intimal thickening in the stented segments of several bypass grafts that have been surgically retrieved or obtained by atherectomy 1 to 5 months after stent implantation.[15] By diminishing the formation of early occlusive thrombus with more effective anticoagulation, the residual nonoccluding thrombus could form the substrate for late restenosis. Although the second group had a higher proportion of bailout cases, a previous study from our group did not identify increased relative risk for restenosis from bailout cases compared with primary or restenosed lesions.[16]

The high incidence of late adverse clinical events in patients with stents is a cause for concern. A mortality rate of 9% in bypass grafts and 6.6% in native vessels is higher than in reported angioplasty studies.[17-19] However, it must be stressed that a large number of stents in native vessels were implanted for abrupt closure after angioplasty, which dramatically increases the risk of the procedure.[20] Actuarial event-free survival was 37% at 20 months in patients who had had bypass surgery and 46% at 40 months in native vessels. In the bypass group, about 30% of the adverse events were unrelated to the stented lesion and were due to worsening of a different lesion or to development of new lesions. In the native vessel group, 12% of the adverse events were unrelated to the stented lesion. In addition, 9 of the 30 bypass operations in patients with stented native vessels were performed as part of a protocol for patients stented for the bailout indication.[20] Although there are no comparable series of patients with stented native vessels in the literature because of the unique set of indications in our study, 3 recent reports have been published on late clinical follow-up after angioplasty in bypass grafts. The Thoraxcenter reported that only 41% of patients were alive and event-free (myocardial infarction, repeat bypass surgery, repeat angioplasty) at a median follow-up of 2.1 years.[21] A review of the overall Dutch experience also showed limited late beneficial results with a 2- and 5-year event-free survival of 52 and 26%, respectively, in 454 patients who underwent bypass surgery.[22] Webb et al[11] described a 71% freedom from death, infarction and surgery at 5 years in bypass patients who underwent angioplasty at their institution, but did not include the 27% incidence of second angioplasty procedures also required in their patient group. However, our study was not a randomized trial designed to compare stenting with angioplasty, but rather an observational study with a first-generation coronary stent. Nevertheless, all of these late follow-up studies of nonoperative coronary revascularization clearly show that these are palliative procedures and not long-term solutions to the underlying problems of progression of underlying coronary disease and iatrogenically induced restenosis.

Several important points emerge from this study. Although in-hospital occlusion rates improved in the later experience, thrombosis of the Wallstent continues to limit its use. Restenosis rates with the 50% diameter stenosis criterion do not seem to be significantly improved when compared with historical results after angioplasty, although definitive statements must await randomized trials. Bypass grafts, in particular, had a high incidence of late restenosis, although early occlusion occurred less significantly than in native vessels. There is insufficient evidence at this time to implant a coronary stent outside of a randomized trial with the following exceptions: (1) bailout for abrupt occlusion; (2) suboptimal (inadequate dilatation) results after angioplasty; and (3) bypass grafts at high risk (e.g., friable lesions) for distal embolization with angioplasty that may benefit from the scaffolding property of the Wallstent.

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APPENDIX

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Effects of the Dipyridamole Test on Left Ventricular Function in Coronary Artery Disease

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The dipyridamole stress test is used with thallium-201 to detect areas of inhomogeneity of blood flow that point to coronary artery disease (CAD). It is unclear whether dipyridamole produces inhomogeneous perfusion only or whether it actually decreases net flow in the obstructed vessels and produces true ischemia. It is also unclear what effect dipyridamole has on global and segmental left ventricular function. Therefore, ejection fraction, segmental wall motion and ventricular volume equivalents were measured before and after dipyridamole in 113 patients and 32 normal subjects. Ejection fraction responded in an abnormal fashion in 98 patients (87%), decreasing from 49 ± 11% to 43 ± 13% ($p < 0.0001$), whereas it increased in 29 normal subjects (90%) from 57 ± 6% to 64 ± 10% ($p < 0.0001$). Wall motion worsened distinctly in 75 patients (66%), and pressure/volume ratio deteriorated in 72%. The effect of dipyridamole lasted between 10 and 25 minutes, but was promptly reversed by aminophylline. These findings indicate that dipyridamole generally induces true ischemia in CAD. Furthermore, the degree of dysfunction is related to the angiographically assessed severity of CAD. The shortness of breath (seen in 10% of patients) may be partially explained by the findings, and it seems advisable to give aminophylline to every patient in order to promptly correct left ventricular dysfunction.

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The dipyridamole test is now used universally in conjunction with thallium-201 scintigraphy.[1-6] It is not clear whether dipyridamole affects left ventricular (LV) function or not. LV function could become depressed if dipyridamole induces sufficient shunting away of blood from significantly stenotic vessels. However, if the drug selectively increases perfusion through the normal vessels without substantially reducing perfusion in the stenotic arteries, segmental function would remain normal in the jeopardized segments. Furthermore, because dipyridamole produces generalized vasodilation and afterload reduction, LV unloading may improve enough to mask whatever negative effects the drug may have exerted on the myocardium. Therefore, we present data obtained prospectively in a large number of subjects, which indicate that dipyridamole indeed induces ischemia that is sufficiently significant to be detected by radionuclide ventriculography as LV dilatation and dysfunction.

METHODS

Study population: A group of 145 consecutive subjects who met the criteria described later entered the study and were classified as having either "low likelihood" of coronary artery disease (CAD) (group I) or "certain" CAD (group II).

Low likelihood of coronary artery disease (group I): Group I comprised 32 subjects (23 men and 9 women, mean age 59 years, range 40 to 76) referred because of nonspecific, noncardiac chest pain that was not retrosternal, was unrelated to exertion or emotion and was relieved by neither rest nor nitroglycerin. No subject was receiving cardiac medications. All subjects had normal cardiac examination, resting electrocardiogram and normal thallium-201 scintigraphy. Two-dimensional echocardiography was normal in all except 2 patients who had mild LV hypertrophy and dilation. Coronary angiography performed after the radionuclide studies showed normal coronary arteries in 12 patients, and obstructions of <50% in 2.

Coronary artery disease group (group II): Group II comprised 113 patients (101 men and 12 women, mean age 59 years, range 41 to 81) referred because of typical effort angina pectoris relieved by rest and nitroglycerin, and related to exertion or emotion. Myocardial infarction was documented in 71 patients. Coronary angiography demonstrated >60% obstruction in 1 vessel in 19 patients, in 2 vessels in 32, and in 3 vessels in 19.

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Coronary artery bypass surgery had been performed in 15 patients and coronary angioplasty in 4, but angina pectoris was still present or had recurred in all except 4. In 112 patients, thallium-201 scintigraphy showed decreased thallium uptake in ≥ 1 myocardial segment, with improvement in all except 9 patients; in 1 patient with a 60% left anterior descending artery obstruction, scintigraphy showed normal perfusion.

The decision to perform catheterization and surgery was independent of the results of this study, and catheterization findings were unknown at the time of radionuclide studies. All antianginal medications except sublingual nitrates were stopped ≥ 2 days before the studies. Patients with recent (12 weeks) myocardial infarction, asthma or receiving theophylline maintenance were excluded. All patients gave informed consent, and the study protocol was approved by the institutional Helsinki committee.

Study protocol: Radionuclide ventriculography was performed as previously described.[7,8] Control nuclide count acquisitions were performed twice (before dipyridamole and after a 20-minute rest on a comfortable table). Thus, very close correspondence of the LV volumes and ejection fractions was obtained in all 145 pairs of control studies.

Dipyridamole was infused (0.56 mg/kg over 4 minutes) through an antecubital vein under constant electrocardiographic monitoring and blood pressure measurement. A third nuclide acquisition was then begun, usually 1 minute after dipyridamole infusion. An increase in heart rate of ≥ 5 beats/min was consistently noted in all cases, indicating that dipyridamole had exerted its effects, and this was the time we chose to evaluate the effect of dipyridamole on LV function. Aminophylline was then slowly injected intravenously in 126 subjects (125 to 375 mg). A fourth nuclide acquisition was then performed to detect possible changes in LV function after aminophylline. In 3 normal subjects and 7 patients, the administration of aminophylline was withheld, and serial nuclide studies were performed every 5 minutes to determine the duration of action of dipyridamole on LV function.

The following parameters of LV function were examined: diastolic and systolic volume equivalents,[8,9] segmental wall motion, ejection fraction and end-systolic pressure/volume ratios.[10]

A subset of 30 patients also underwent nuclide ventriculography during rest and graded supine bicycle exercise. Control nuclide acquisition was obtained after the subject's feet were placed in the pedals. Exercise was performed in incremental stages of 25 W at a pedaling rate of 60 rpm. Nuclide acquisition for the exercise study was performed at the stage of maximal tolerable work load. These 2 rest and exercise studies were then compared with the control and dipyridamole studies.

Ejection fraction was calculated from background-corrected end-diastolic and end-systolic counts. End-diastolic volume equivalent was calculated by the following equation[9]:

$$\text{Volume} = \frac{\text{Nuclide counts} \times 0.04\ \text{s/HB} \times \text{frame time}}{\text{Counts in 4 ml whole blood in 60 seconds}}$$

where HB = heart beats. End-systolic volume equivalent was calculated from the end-diastolic volume equivalent and ejection fraction.

Pressure/volume ratio was calculated as the ratio of arm-cuff systolic blood pressure to end-systolic volume, obtained before and after dipyridamole. The response to dipyridamole was then calculated according to the formula of Dehmer et al[10,11]:

$$\text{RD} \cdot \text{P/V} = \frac{\text{Dipyridamole P/V ratio}}{\text{Control P/V ratio}}$$

where RD = response to dipyridamole, P = pressure, and V = volume. A number >1 indicates improvement, whereas a result <1 indicates deterioration in systolic LV function.

Regional wall motion was analyzed in the 45-degree left anterior oblique position and graded on a 6-point scale: 4 = hyperkinetic; 3 = normal; 2 = mildly hypokinetic; 1 = severely hypokinetic; 0 = akinetic; and −1 = dyskinetic. The left ventricle was divided in 3 segments: anteroseptal, inferoapical and posterolateral. "Paradox" images were developed by a computer program to enable additional visual estimation of regional dyskinesia.

Peripheral venous nuclide counts: It was suggested that increased sympathetic tonus alters the number of red blood cells in the circulation and introduces possible errors in volume estimation.[12] Therefore, the radioactivity of equal volumes of blood obtained from 10 patients before and after dipyridamole was analyzed.

Coronary angiography: Coronary angiograms were analyzed by consensus of 3 cardiologists independent of the radionuclide studies. The number, location and percent diameter narrowing (analyzed by calipers) of coronary lesions were used to describe the extent and severity of CAD. Stenoses >60% were defined as "significant." Subjects were defined as "normal" if the arteries were entirely normal or if observed stenoses were <50% (2 cases).

Statistical analysis: Heart rate, blood pressure, LV ejection fraction, volume equivalents and wall motion before and after dipyridamole were analyzed by the paired 2-tailed *t* test, and the unpaired *t* test was used for the pressure/volume ratio response to dipyridamole. Results were considered to be statistically significant at $p < 0.05$. Baseline ejection fraction was calculated for all 145 pairs of control measurements as the average of the 2 control measurements. Changes in ejection fraction were calculated as absolute units of change from this average value (e.g., from 50 to 30% = 20 U). Changes in LV volume equivalents were normalized by handling increments or decrements as percent deviations from the baseline. The relation between changes in ejection fraction during exercise and after dipyridamole was calculated by Pearson's coefficient of correlation. The relation of the ejection fraction response to severity of CAD was analyzed by 1-way analysis of variance with the SPSS/PC Statistical Analysis Package.[13]

RESULTS

Control left ventricular ejection fraction: The control ejection fraction values were almost identical, as specified by the protocol. For the 113 pairs of control studies in the 113 CAD patients, the 2 mean ejection fraction values were 48.3 ± 11.5 and 48.4 ± 11.6%, the maximal difference between 2 of any pair of values was 4% (in only 1 patient), the mean difference was 1.5% and the intraobserver variability was 0.5%.

Heart rate, blood pressure and symptoms after dipyridamole: Heart rate increased consistently in all patients (mean 80 ± 10 vs 74 ± 10 beats/min; $p < 0.005$). Blood pressure decreased from 142 ± 12/83 ± 10 to 135 ± 10/81 ± 9 mm Hg ($p < 0.05$). Dipyridamole caused chest pain in 56 patients, ST depression in 18, and atrial or ventricular extra-systole in 2. Thirteen CAD patients reported shortness of breath; no wheezing was detected on auscultation.

Response of ejection fraction to dipyridamole (Figure 1): Ejection fraction increased in 29 of 32 (90%) normal subjects (≥5 U in 16 [69%], and >10 U in 6 of these [26%]; <5 U in 5 [22%]). Ejection fraction did

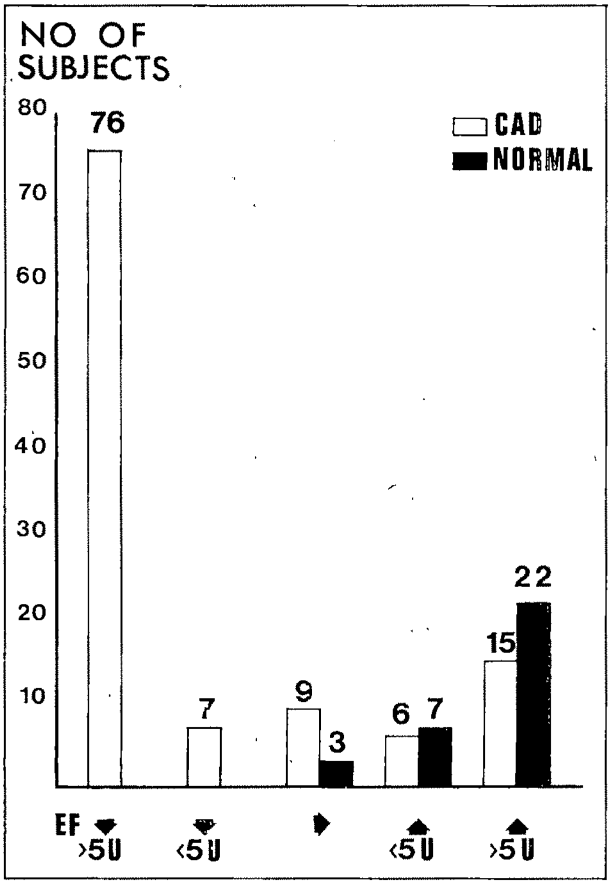

FIGURE 1. Bar graph showing number of abnormal and normal ejection fraction (EF) responses of 113 patients with coronary artery disease (CAD) and 32 normal subjects to dipyridamole. Abnormal response is defined as increase in ejection fraction of <5 U, decrease or no change.

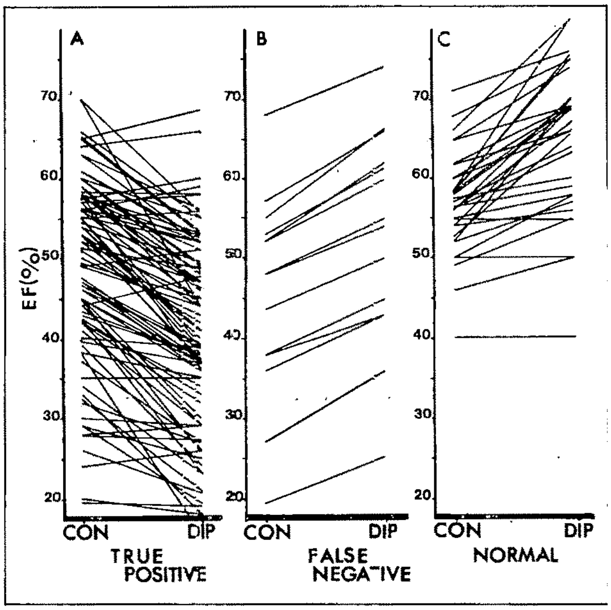

FIGURE 2. Individual responses of 113 patients with coronary artery disease (*A and B*) and 32 normal subjects (*C*) to dipyridamole (DIP). *A* shows the 98 abnormal (true positive) responses (i.e., either decrease in ejection fraction, no change or increase of <5 U). *B* presents the only 15 patients with coronary artery disease who responded by increasing ejection fraction in normal fashion (false negative response) (i.e., increase of ≥5 U). CON = control.

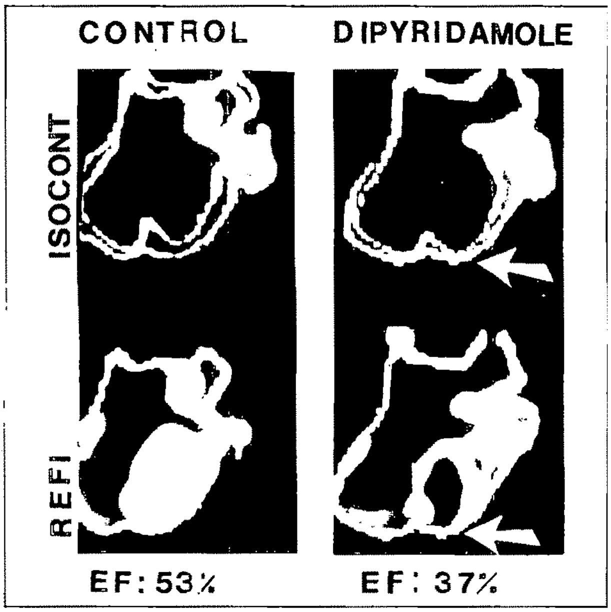

FIGURE 3. Response to dipyridamole in patient with coronary artery disease (CAD) with normal ejection fraction (EF) of 53% in the control state. After dipyridamole, ejection fraction decreased to 37%. Each *panel* presents diastolic and systolic left and right ventricular isocontour (ISOCONT) at *top*, and regional ejection fraction image (REFI) at *bottom*. Degree of regional wall motion is visually represented in REFI mode by computer-derived amount of *white shading*. Increase in left ventricular systolic dimension after dipyridamole is clearly seen in *top isocontour section*, whereas diffuse decrease in segmental wall motion is depicted in *bottom* by sharp decrease in *white shading*. *Arrows* point to inferoapical akinesia induced by dipyridamole.

not increase in 2 normal subjects, and did not decrease in any. In contrast, ejection fraction decreased ≥5 U in 76 of 113 (67%) patients in group II, and <5 U in another 7; thus, it decreased after dipyridamole in 83 patients (73%), decreasing >10 U in 41 (36%). Ejection fraction did not change in 9 patients, and increased <5 U in 6. An increase of ≥5 U was seen in only 15 patients (13%) (Figure 1). Thus, if an increase in ejection fraction of ≥5 U is the minimal increase needed to define a response to a stress modality as normal (as is customary in exercise testing), as many as 98 CAD patients (87%) exhibited an abnormal response to dipyridamole. Only 13% of these patients had a false negative response.

Mean ejection fraction increased from 57 ± 6 to 64 ± 10% ($p < 0.0001$) in group I, whereas it decreased from 49 ± 11 to 43 ± 13% ($p < 0.0001$) in group II. Patients with ejection fractions > or <50% responded to dipyridamole with a similar decrease in ejection fraction (13 and 11.5%, respectively; p = not significant). Individual responses to dipyridamole are shown in Figure 2; an example is illustrated in Figure 3.

Pressure/volume ratio response (Figure 4): Pressure/volume ratio increased, signaling improved LV function in 69% (18 of 26) of normal subjects, whereas it decreased (LV dysfunction) in 72% (64 of 88) of CAD patients. Mean response of pressure/volume ratio was 1.58 ± 0.68 (improved function) for normal subjects and 0.82 ± 0.38 (depressed function) ($p < 0.0001$) for CAD patients.

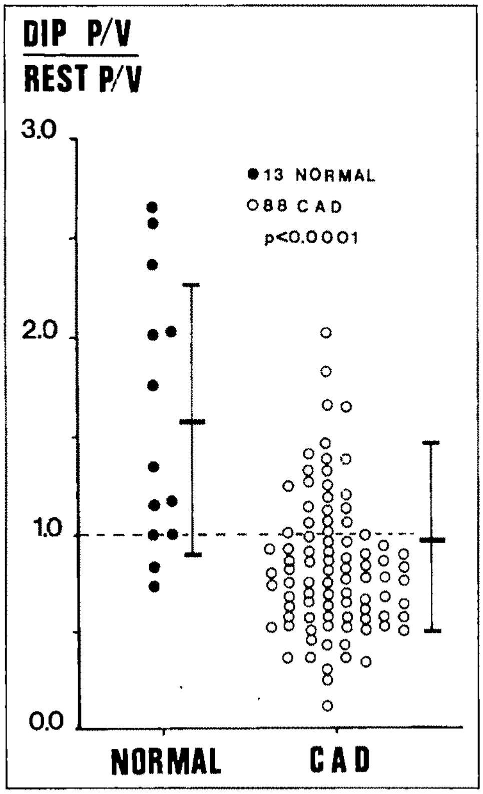

FIGURE 4. Response of pressure/volume (P/V) ratio to dipyridamole (DIP), expressed as ratio of systolic pressure/volume after dipyridamole divided by same value obtained at rest (see Methods). *Dashed line* divides responses as either improvement (>1) or depression (<1) of pressure/volume ratio. CAD = coronary artery disease.

Duration of dipyridamole effect (Figure 5): The change in ejection fraction persisted for 10 to 25 minutes in the 10 subjects in whom the administration of aminophylline was postponed or withheld.

Changes in volume equivalents: Mean end-diastolic volume equivalent increased by 19%, and mean end-systolic volume equivalent by 43% ($p < 0.005$) in CAD patients. In contrast, these 2 measurements decreased by 8 and 23%, respectively, in normal subjects ($p < 0.005$).

Changes in segmental wall motion: Mean segmental wall motion score decreased from 7.1 ± 2.3 to 5.6 ± 2.5 ($p < 0.05$) in CAD patients. This worsening in wall motion was noticeable in 75 of 113 (66%) patients and was very marked (≥3 U) in 26 of these 75 (35%).

Comparison of exercise and dipyridamole (Figure 6): Excellent correlation in the direction of change in ejection fraction was observed; it decreased or remained unchanged in both testing modalities in 22 patients and increased in both by >5 U in 4 patients. Poor correlation was seen in only 4 patients, mostly due to inade-

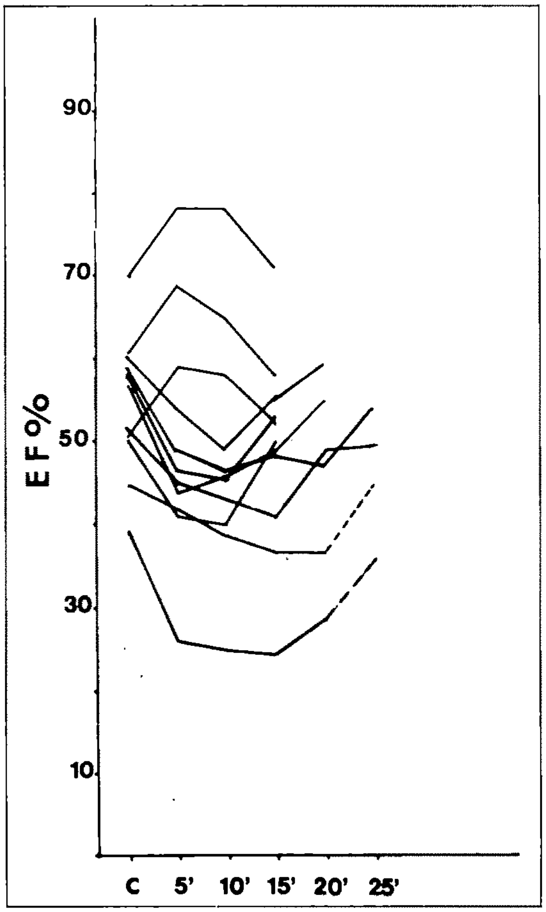

FIGURE 5. Time course of dipyridamole effect on ejection fraction (EF) in 3 normal subjects (increase) and 7 patients (decrease). Effect persisted for 10 minutes, and in some cases for 20 and 25 minutes. *Dashed line* indicates return to baseline values after administration of aminophylline to alleviate chest pain.

quate exercise performance, which did not produce an increase in ejection fraction in 3. Mean ejection fraction decreased from 54 ± 9 to 50 ± 14% with exercise and from 53 ± 9 to 49 ± 14% after dipyridamole ($r = 0.686$; $p < 0.0005$).

Correlation with severity of coronary artery disease (Figure 7): Coronary cineangiography was performed in 70 patients: 19 had 1-vessel (left anterior descending artery in 11, right coronary in 4, circumflex in 2), 32 had 2-vessel, and 19 had 3-vessel diseases. Mean ejection fraction decreased in each of these subgroups, with the decrease being much more marked in the 3-vessel (9.2 U) than in the 1-vessel (2.6 U) disease subgroup. The decrease in ejection fraction in the 2-vessel subgroup was not significantly different from that of the 1-vessel subgroup. The proportion of patients with abnormal (true positive) responses to dipyridamole was substantially smaller (13 of 19, 68%) in the 1-vessel subgroup than in the other 2 subgroups (30 of 32 [93%] and 19 of 19 [100%]). Conversely, proportionately more patients with 1-vessel disease increased their ejection fraction (6 of 19, 32%) than in the 2-vessel (3 of 32, 9%) and 3-vessel (0 of 19, 0%) disease subgroups.

Coronary arteries were normal in 14 subjects at cineangiography. Twelve subjects responded to dipyridamole with increased ejection fraction (59 ± 8 to 66 ± 11%; $p < 0.05$), whereas 2 (hypertensive) subjects had no increase.

Response to aminophylline (Figure 8): Ejection fraction, LV volume equivalents and heart rates promptly returned to baseline values in all patients within 1 to 3 minutes after administration of aminophylline, simultaneously with relief of chest pain and dyspnea. Mean ejection fraction of group II returned to 49 ± 12% after aminophylline.

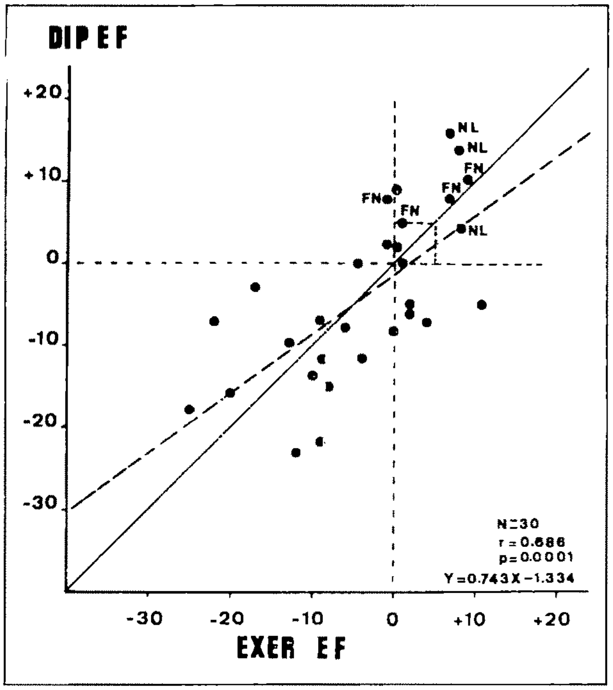

FIGURE 6. Correlation of changes in ejection fraction (EF) after supine exercise (EXER) testing and dipyridamole (DIP) in 30 subjects. Direction in change of ejection fraction is concordant in 26 subjects.

Peripheral venous radionuclide counts: There was no difference in peripheral counts in the 10 patients whose blood was analyzed before and after dipyridamole (7,575 ± 3,692 Kcounts vs 7,525 ± 3,594). Thus, the changes in LV volumes were not due to alterations in blood radioactivity from increased sympathetic tonus.

DISCUSSION

Dipyridamole causes true ischemia: In the present study, we offer clear evidence from a large cohort that the response of CAD patients to dipyridamole is distinctly different from that of normal subjects. In the latter, LV function improves as a result of peripheral vasodilation (unloading effect) and increased sympathetic tone. In CAD, in contrast, dipyridamole causes distinct LV dilatation and dysfunction that may last for as long as 20 to 25 minutes. Thus, the clear conclusion

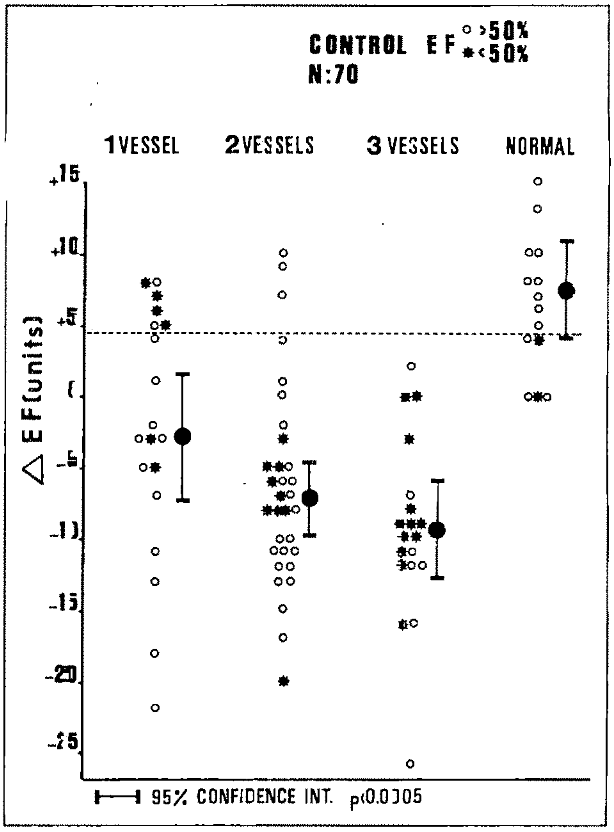

FIGURE 7. Changes in ejection fraction (EF) in each subset of 1-, 2- and 3-vessel disease, and in 14 subjects with normal coronary arteries. Statistically significant difference was seen between degree of depression of ejection fraction in subsets with coronary artery disease and improvement seen in normal subjects. There is a greater proportion of falsely normal responses in patients with 1-vessel than in those with 2-vessel disease (6 of 19 vs 3 of 32), whereas there are none in the 3-vessel disease subset. The response of patients with 1-vessel disease is statistically different from that of those with 3-vessel disease. Response of patients with 2-vessel disease is of borderline significance. *Dashed line* divides normal from abnormal responses. INT. = interval.

is that dipyridamole causes true ischemia in a high number of patients with documented CAD. This conclusion concurs with the echocardiographic findings of Picano et al[14] and Bolognese et al,[15] and with the more recent findings of Cates et al[16] who, using radionuclide ventriculography, also demonstrated a high incidence of wall motion abnormalities and abnormal ejection fraction responses to dipyridamole in 21 CAD patients. The doses of dipyridamole used by Cates (0.725 mg/kg) and Picano (0.84 mg/kg) were high, and our study indicates that LV dysfunction is also demonstrable at the standard dose.

Chouraqui et al[17] also demonstrated LV dilatation by thallium-201 scintigraphy during dipyridamole. Even more recently, Jain et al[18] also showed transient development or worsening of wall motion abnormalities by 2-dimensional echocardiography in patients with transient perfusion defects after dipyridamole. These studies are all consistent with the hypothesis that true ischemia is indeed very often induced by dipyridamole in CAD. The findings of 2 previous radionuclide ventriculographic studies do not seem to fit this theory: Harris et al[19] reported that only 13% of 15 patients developed abnormal wall motion after dipyridamole, and Sochor et al,[20] using a very strict criterion to define an abnormal response to dipyridamole (decrease >8 U), found only a 31% sensitivity for CAD. Thus, these 2 studies seem to be at odds with the hypothesis that dipyridamole acts by producing ischemia, but the number of patients tested was small in both studies. In addition, the criteria used by Sochor to define an abnormal response to dipyridamole are probably too exigent. Finally, if the cohort is comprised in large part of patients with 1-vessel disease, as in the study of Sochor, many patients may indeed not show an abnormal response, as was the case in our study and that of Cates et al.[16]

Correlation with severity of coronary artery disease: It is clear from Figure 7 that the more extensive CAD is, the greater the likelihood of an abnormal response to dipyridamole. The sensitivity of dipyridamole-nuclide ventriculography, if the ejection fraction response to dipyridamole were to be used as a screening test for ischemia, would be relatively low (70%) in 1-vessel disease, but would be high in 2-vessel (93%) and 3-vessel (100%) disease.

The mean decrease in ejection fraction with dipyridamole is also more marked in the presence of 3-vessel disease, but it is noteworthy that extreme depression of ejection fraction (≥15 U) was seen equally in all 3 groups.

Influence of aminophylline: Aminophylline completely inhibits the coronary vasodilation induced by dipyridamole.[21] The present study demonstrates that the LV dysfunction induced by dipyridamole is promptly reversed by aminophylline.

Study limitations and implications: This study population is heterogeneous, comprised as it is of patients with a wide range of control ejection fraction, and heterogeneous coronary arterial lesions. Not all subjects underwent coronary angiography. The findings of this study may not be used to predict with full confidence the severity of CAD in any particular patient. However, despite these limitations, the important fact remains that there is overall a major difference in the response to dipyridamole of CAD patients compared with that of normal subjects: LV function almost uniformly improves in the latter because of the change in unloading conditions and the reflex increase in sympathetic tone. In contrast, LV dysfunction tends to occur in CAD, particularly in 2- and 3-vessel disease. The degree of LV dysfunction is sometimes striking, and the duration of this effect (up to 25 minutes) is substantial. Some patients (10% in this series) report dyspnea during the test,[22] and it is tempting to attribute this to the LV dysfunction that appears rapidly and persists for some time. Dyspnea consistently disappears after aminophylline simultaneously with the improvement in LV function. Therefore, we think that it is advisable to administer aminophylline to all patients in order to abort this potential hemodynamic deterioration.

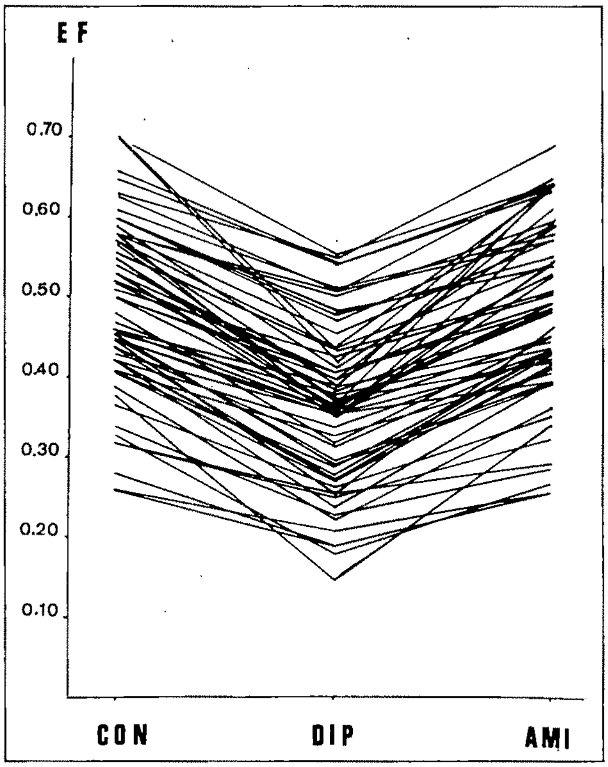

FIGURE 8. Immediate correction of ejection fraction (EF) brought about by aminophylline (AMI) in patients with coronary artery disease in whom dipyridamole (DIP) had depressed it. CON = control.

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Improvement in Left Ventricular Systolic Function After Successful Radiofrequency His Bundle Ablation for Drug Refractory, Chronic Atrial Fibrillation and Recurrent Atrial Flutter

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Incessant supraventricular tachyarrhythmia may lead to a reversible impairment of left ventricular (LV) function. This issue was investigated in 10 patients (aged 64 ± 13 years) who underwent radiofrequency His bundle ablation for control of drug refractory, chronic atrial fibrillation (n = 9) and recurrent atrial flutter (n = 1). LV function was assessed by 2-dimensional guided M-mode echocardiography within 24 hours (baseline) and 49 ± 18 days (follow-up) after successful ablation, both during VVI pacing at 70 beats/min.

Fractional shortening increased from 28 ± 9% at baseline to 35 ± 8% at follow-up (p = 0.006). This increase in fractional shortening was due to a significant reduction of end-systolic diameter from 41 ± 10 to 36 ± 10 mm (p = 0.02), whereas there was no appreciable change in end-diastolic diameter (56 ± 7 to 55 ± 10 mm; p = 0.5). These changes were substantially greater in patients with baseline impairment of LV function (fractional shortening <27%). Fractional shortening increased by 12% (p = 0.14) in patients with normal LV function (n = 5) and by 44% (p = 0.02) in those with impaired LV function at baseline (n = 5). The greater increase in fractional shortening in patients with preexisting LV impairment was due to a more pronounced decline in end-systolic dimensions (−11.9%; p = 0.08) compared with that of patients with normal LV function at baseline (−9.21%; p = 0.2). End-diastolic diameter showed no significant change in either group (−3.53% [p = 0.8] and −0.58% [p = 0.4]).

These data show that chronic, rapid atrial fibrillation and flutter may lead to impairment of LV systolic function, which is reversible on control of the tachycardia by radiofrequency His ablation. The recovery of LV mechanics is substantially greater in patients with the more profoundly depressed LV function at initial evaluation.

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Evidence has accumulated that chronic uncontrolled supraventricular tachycardia may result in reversible left ventricular (LV) dysfunction.[1-16] Reports in support of this hypothesis mainly relate to the observed improvement in LV function after successful correction of ectopic atrial,[2,5,10,11,16] junctional[12] and circus movement[1,2,9] tachycardia, and occasionally by control of atrial fibrillation (AF).[8,14,16] Whereas Philips and Levine[8] observed a normalization of cardiac silhouette on chest x-ray, and Kay et al[14] reported a substantial improvement in quality of life and exercise capacity after correction of AF, LV function in patients with AF was not directly quantified by these investigators. In the present study we report a substantial improvement in systolic ventricular function after control of rapid AF by radiofrequency His bundle ablation. If baseline LV measurements are obtained early after this procedure, His bundle ablation offers the unique possibility to study the genuine LV depressant effect of atrial tachyarrhythmias independent of the potentially confounding influence of rate, drugs or direct-current interventions.

METHODS

Patients: The study group comprised 10 patients (8 men and 2 women, aged 64 ± 13 years, range 49 to 82) referred to our institution for atrioventricular (AV) junctional ablation of drug refractory, nonparoxysmal AF (9 patients) and frequent episodes of sustained (>24 hours) atrial flutter (1 patient). Patients were prospectively selected by the ability to obtain high-quality echocardiographic recordings and by the absence of regional wall motion abnormalities, left bundle branch block[17] and significant valvular heart disease.

All patients had been taking a variety of unsuccessful drugs including digitalis, verapamil, sotalol, several β blockers and combinations of these. Two patients had prior direct-current ablation of the AV junction, but were referred for resumption of AV conduction. The ventricular response was >120 beats/min most of the day, with peak ventricular rates of 150 to 200 beats/min in patients with AF. The typical rate in the patient with sustained atrial flutter was 160 beats/min.

Ablation procedure: A temporary lead was inserted through the left subclavian vein for backup VVI pacing in patients who were not supplied with a permanent pacemaker previously. The HAT200 generator (K.

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Osypka, Grunzbach-Wyhlen, Germany) and a steerable catheter were used for unipolar, temperature-guided radiofrequency His bundle ablation. The ablation end points were (1) production of complete AV block, and (2) AV node modulation reflected by a ventricular response <120/min during pharmacologic stress.

Orciprenaline testing: Each patient underwent pharmacologic stress testing immediately after successful ablation. For this, orciprenaline (25 to 50 μg/min) was infused over 30 minutes. A successful ablation was defined as (1) persistence of complete AV block despite pharmacologic challenge and (2) a ventricular rate consistently <120 beats/min during infusion of orciprenaline if AV conduction resumed. The ablation procedure ended if 1 of the criteria was met. The orciprenaline test was then repeated 24 hours after ablation, and if AV block or modulation persisted, the patient was supplied with a rate-responsive pacemaker. The patient with atrial flutter had a DDD system implanted.

Echocardiographic follow-up: High-quality 2-dimensional and 2-dimensional-guided M-mode echocardiograms were obtained within 24 hours after ablation during temporary right ventricular pacing at 70 beats/min (baseline evaluation). At long-term echocardiographic follow-up, the permanent pacemaker was programmed to the VVI mode, and the ventricular pacing rate was fixed at 70 beats/min. All echocardiograms were obtained by the same investigator. M-mode measurements of end-diastolic and end-systolic dimensions were performed according to the recommendations of the American Society of Echocardiography.[18,19] Fractional shortening was calculated as follows: [(end-diastolic − end-systolic dimension)/end-diastolic dimension] • 100. No patient was receiving antiarrhythmic drugs during baseline or follow-up echocardiographic studies.

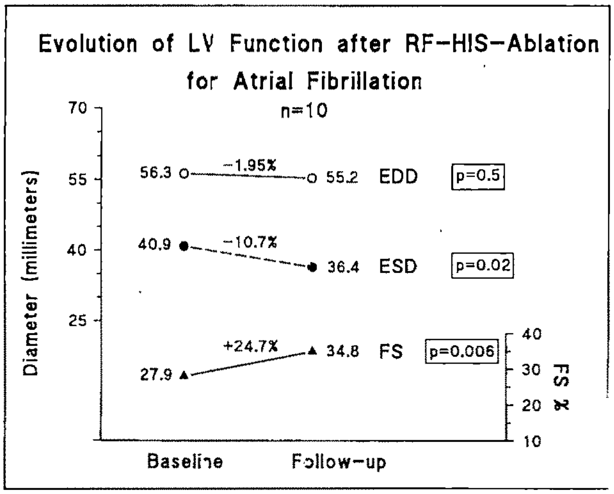

FIGURE 1. Synopsis of percent changes in fractional shortening (FS), and end-diastolic and end-systolic diameters. There is significant increase in fractional shortening, mainly resulting from corresponding significant decline in end-systolic dimensions (ESD). No significant change in end-diastolic dimensions (EDD) was observed. LV = left ventricular; RF = radiofrequency.

Data analysis: Comparisons were obtained by paired and unpaired Student's *t* tests, as appropriate. Data are expressed as mean ± standard deviation.

RESULTS

Ablation end points: Complete AV block was achieved in 8 patients, whereas 2 fulfilled the criteria for successful AV nodal modulation. The ventricular rate in these patients was lower than the pacemaker escape interval, thus enabling echocardiographic measurements under the aforementioned controlled conditions. There were no significant ventricular arrhythmias during ablation, and no patient needed defibrillation.

Echocardiographic follow-up: Follow-up echocardiograms were obtained a mean of 49 ± 18 days (range 26 to 77) after ablation. There was a significant improvement in fractional shortening (Figure 1). This increase in fractional shortening was almost exclusively due to a corresponding decline in end-systolic dimension, whereas there was no appreciable change in end-diastolic diameter (Figure 1).

In individual terms, an increase in fractional shortening was observed in 9 of 10 patients (Figure 2). In 5 patients, LV function at baseline, although markedly depressed, was still within normal limits (fractional shortening >27%; group 1); it was impaired (fractional shortening ≥27%; group 2) in the remaining 5 (Figure 2). Whereas fractional shortening at baseline was significantly different between groups 1 and 2 (35 ± 5 vs 21 ± 4%; p = 0.003), it did not differ significantly at fol-

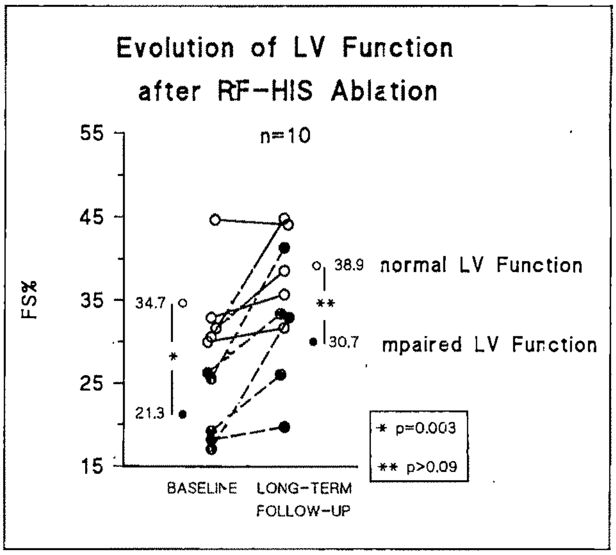

FIGURE 2. Increase in fractional shortening (FS) after successful control of tachycardic atrial fibrillation by radiofrequency (RF) His bundle ablation. Baseline recordings were obtained within 24 hours after ablation, and follow-up echocardiograms a mean of 48.9 days after. Note that FS increased in 9 of 10 patients and that 3 of 5 with depressed myocardial function (FS <27%; *full circles*) at baseline normalized within time frame evaluated. Consequently, FS between groups was significantly different at baseline, but not at follow-up. Increase in FS was statistically significant in patients with impaired (p = 0.02) but not in those with normal left ventricular (LV) function (p = 0.14).

low-up (39 ± 5 vs $31 \pm 8\%$; $p = 0.09$). Serial changes in fractional shortening were significant in group 2 ($p = 0.02$), but not in group 1 ($p = 0.14$). In the patient with recurrent, sustained atrial flutter, fractional shortening increased from 32 to 39%.

Three of 5 patients in group 2 had normal fractional shortening within 31, 57 and 59 days, respectively (Figure 2), and the average increase in fractional shortening was 44% in group 2 compared with 12% in group 1.

The greater increase of fractional shortening in group 2 was due to a corresponding greater decline in end-systolic dimensions in this group (49 ± 6 vs 43 ± 10 mm, -11.9%; $p = 0.08$). End-systolic dimensions declined by 9.2% in group 1 (33 ± 3 vs 30 ± 5 mm; $p = 0.2$). Intergroup differences in end-systolic dimensions were significant at baseline and follow-up ($p = 0.0015$ and 0.044, respectively).

There was no appreciable change in end-diastolic dimensions within the time frame evaluated in either group (group 1: 51 ± 3 vs 49 ± 6 mm; group 2: 62 ± 6 vs 61 ± 9 mm [at baseline and follow-up, respectively]). Significant intergroup differences were obtained at baseline and follow-up ($p = 0.009$ and 0.03, respectively).

DISCUSSION

This study indicates that improvement of systolic LV function may be expected in patients with incessant, rapid AF and in those with frequent episodes of recurrent atrial flutter after control of the pertinent arrhythmias. This improvement is more distinct in patients with more profoundly depressed LV function at baseline.

Our data extend previous observations on reversible LV dysfunction in patients with ectopic atrial, junctional and circus movement tachycardia.[1,2,5,9-12,16] Furthermore, by quantifying these changes in LV performance, this study offers additional explanation for the previously reported increase in quality of life and exercise capacity after correction of AF by AV junctional ablation.[14] Most important, our results are not confounded by differences in rate, but rather reflect entirely improved muscle function, since baseline measurements were obtained after ablation and thus after successful control of rapid AF.

The observed increase in fractional shortening was mainly due to a decline in end-systolic dimension, whereas the end-diastolic diameter was not significantly changed. This was previously noted. Cruz et al,[1] performing serial M-mode measurements in patients with surgically corrected supraventricular tachycardia, found a significant decrease in end-systolic diameter within 21.6 months, whereas end-diastolic dimension did not change significantly within that time. Likewise, Damiano et al,[13] in 13 dogs paced chronically at a rate of 190 beats/min, observed a normalization of the ejection fraction within 2 weeks, whereas end-diastolic volumes remained elevated for as long as 3 months. Reversible depletion of high-energy substrates has been suggested as the possible mechanism of such pacing-induced LV dysfunction.[15] However, the precise mechanism of such reversible myocardial dysfunction remains to be fully elucidated.

Currently, there is no evidence that radiofrequency energy may impair LV performance, whereas direct-current ablation at high-current densities may cause myocardial depression and electromechanical dissociation.[20-22] Therefore, only patients who underwent radiofrequency ablation were eligible for the study.

The potential limitations of determination of LV function in patients with rapid AF, and the limitations of M-mode measurements are well-known. However, we believe that we were able to circumvent major limitations for several reasons. First, we performed baseline M-mode measurements after ablation rather than before the procedure during tachycardic AF. Second, both baseline and follow-up measurements were obtained at the same paced rate of 70 beats/min. Third, all patients served as their own controls, and baseline and follow-up measurements were obtained under the same conditions. Therefore, abnormal septal motion during right ventricular pacing[23] should be of minor significance to our results. Finally, the evaluation of baseline myocardial function within 24 hours after control of AF seems applicable, because substantial change in myocardial mechanics may not be expected until the tenth day after abolition of the tachycardia.[2,3] However, as a consequence, the beneficial effect of radiofrequency ablation on LV function cannot be fully assessed for some time after ablation.

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Frequency of Recurrent Atrial Fibrillation After Catheter Ablation of Overt Accessory Pathways

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The effect of successful catheter ablation of overt accessory pathways on the incidence of atrial fibrillation (AF) was studied in 129 symptomatic patients with ($n = 75$) or without ($n = 54$) previous documented AF. Fourteen had had ventricular fibrillation. Factors predictive of recurrence were examined, including electrophysiologic parameters. Atrial vulnerability was defined as induction of sustained AF (>1 minute) using single, then double, atrial extrastimuli at 2 basic pacing cycle lengths. When compared to patients with only reciprocating tachycardia, patients with clinical AF included more men (77 vs 54%, $p = 0.008$) and were older (35 ± 12 vs 29 ± 12 years, $p = 0.01$). They had a significantly shorter cycle length leading to anterograde accessory pathway block (252 ± 42 vs 298 ± 83 ms, $p < 0.001$), greater incidences of atrial vulnerability (89 vs 24%, $p < 0.001$) and subsequent need for cardioversion (51 vs 15%, $p < 0.001$). After discharge, the follow-up period was 35 ± 12 months (range 18 to 76): 7 patients with previous spontaneous AF (9%) had recurrence at a mean of 10 months after ablation. Age, presence of structural heart disease, accessory pathway location, atrial refractory periods and accessory pathway anterograde conduction parameters were not predictive of AF recurrence. Persistence of atrial vulnerability after ablation was the only factor associated with further recurrence of AF. Atrial vulnerability was observed after ablation in only 56% of patients with previous AF versus 89% before ablation.

It is concluded that successful catheter ablation of accessory pathways prevents further recurrence of AF in 91% of patients. This result favors the use of ablative procedures in the Wolff-Parkinson-White syndrome.

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Patients with the Wolff-Parkinson-White syndrome may have a variety of paroxysmal tachycardias. Anomalous conduction pathways can either be involved in the reentrant circuit (reciprocating tachycardias) or serve a "bystander" role (atrial arrhythmias) with a ventricular response depending on their functional properties.[1,2] In the first setting, ablation of the accessory pathway leads to the disappearance of tachycardias. In the second, atrial arrhythmias would be expected to recur even after accessory pathway ablation. However, some reports[3-5] suggested a susceptibility to atrial or ventricular arrhythmia linked to the presence of accessory pathway, and Sharma et al[3] showed that surgical ablation of the accessory pathway prevents further recurrence of atrial fibrillation (AF). To date, catheter ablation is an effective alternative to surgical ablation for the treatment of patients with Wolff-Parkinson-White syndrome.[6-15] In the present study, we report the incidence of AF after successful catheter ablation of the accessory pathway in 129 patients followed up for ≥18 months.

METHODS

Patient population: Data from 129 consecutive patients with inclusion criteria undergoing catheter ablation of an accessory pathway between January 1985 and November 1989 were examined. These patients had the following inclusion criteria: (1) presence of preexcitation during sinus rhythm or atrial stimulation; (2) assessment of atrial vulnerability at the preablation electrophysiologic study; (3) absence of amiodarone therapy during the preceding 6 months; and (4) successful outcome of fulguration, without significant impairment of normal atrioventricular conduction. The study group included 87 men and 42 women (mean age 33 ± 12 years [range 12 to 66]). Seventy-five patients had a past history of at least 1 documented episode of AF. We included in this group 14 patients who had had a cardiac arrest or ventricular fibrillation. The remaining 54 patients only had documented reciprocating tachycardias, which were orthodromic in 52 and antidromic in 2. All patients underwent physical examination, chest roentgenography, 12-lead electrocardiography and 2-dimensional echocardiography. Twenty-six patients underwent coronary angiography and left ventriculography. These data were used to diagnose and classify organic heart disease.

Electrophysiologic studies: After informed consent, all patients underwent intracavitary electrophysiologic study. Antiarrhythmic drugs had been discontinued for ≥5 half-lives. With use of standard catheters, the proto-

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TABLE I Characteristics in Patients with Atrial Fibrillation Compared with Patients with Only Reciprocating Tachycardia

	Reciprocating Tachycardia (n = 54)	Atrial Fibrillation (n = 75)	p Value
Men/women	29/25	58/17	0.008
Age (years)	29 ± 12	35 ± 12	0.01
Presence of cardiopathy (%)	7	12	NS
Accessory pathway location*	11RL 22PS 22LL	16RL 37PS 28LL	NS
Multiple pathways (%)	2	8	0.016
Point of anterograde block (ms)	298 ± 83	252 ± 42	<0.001
Right atrial effective refractory period (ms)	217 ± 20	211 ± 16	NS
Right atrial functional refractory period (ms)	240 ± 18	235 ± 22	NS
Inducible AF (%)	24	89	<0.001
Necessity of electrical shock to interrupt induced AF (%)	15	51	<0.001
Inducibility after ablation (%)	16	56	<0.001
Follow-up (mos)	36 ± 13	34 ± 15	NS
AF recurrence after ablation	0	7	0.02

*Owing to a double accessory pathway in 7 patients, the overall number of accessory pathway locations is greater than the patient number.

AF = atrial fibrillation; LL = left lateral; NS = not significant; PS = posteroseptal; RL = right lateral and anteroseptal.

col for the preablation electrophysiologic study included the following: (1) recording of basic intervals; (2) incremental atrial pacing to atrioventricular block; (3) accessory pathway, atrioventricular nodal and atrial refractory periods at cycle lengths of 550 and 400 ms; and (4) ventricular incremental pacing to ventriculoatrial block. In all patients, assessment of atrial vulnerability was performed by the standard protocol of our laboratory: When pulses of 2 ms duration at twice diastolic threshold were used, a single atrial extrastimulus was delivered on the lateral right atrium at basic cycle lengths of 550 and then 400 ms. In patients in whom AF was not induced, double atrial extrastimuli were then delivered at the same basic cycle lengths. No rapid atrial bursts were performed to define atrial vulnerability. In a previous study,[16] this protocol was found to have a sensitivity of 95%, whereas its specificity in patients without structural heart disease was 87%.[17] In 11 patients, a persistent AF was induced during atrial mechanical stimulation, incremental pacing or by spontaneous degeneration of an induced reciprocating tachycardia. Electrical external cardioversion restored sinus rhythm in 9 patients and was inefficient in 2 (despite several attempts). The protocol to assess atrial vulnerability was performed after electrical cardioversion in all 9 patients. Atrial vulnerability was considered present if a sustained (>1 minute) atrial arrhythmia was induced during the protocol. If induced AF lasted >15 minutes (or degenerated into ventricular fibrillation, n = 3), a cardioversion shock was used to restore sinus rhythm.

Catheter ablation procedure: Follow-up after ablation: The catheter ablation technique was performed using a direct approach.[10,13,14] In all patients, the accessory pathway was ablated as demonstrated by serial electrocardiography, and short- (day 5 to 7, n = 68) or long-term (7 ± 5 months, n = 52) electrophysiologic study. Follow-up electrophysiologic study included atrial incremental pacing to the point of atrioventricular block, ventricular incremental pacing to the point of the retrograde block, and assessment of atrial vulnerability. Results concerning atrial vulnerability were combined whether the study was performed during days 5 to 7 after ablation or later. This combination was thought appropriate because comparison of AF vulnerability in the 13 patients undergoing both the short- and long-term study was concordant in 12 (92%) and discordant in only 1. In these patients, only the long-term results were considered for analysis.

The first 108 patients included in the study were discharged on day 5 without any drug. After a sudden death in June 1989, attributed to a ventricular fibrillation, the other 21 patients were discharged on days 9 or 10 with sotalol (240 to 320 mg) empirically prescribed for the following 6 weeks to reduce the arrhythmogenic risks of fulguration. Therapy with sotalol was begun at day 5 and the QT interval was supervised until discharge.

Most patients were repeatedly examined by cardiologists. All patients complaining of palpitations underwent 24-hour Holter monitoring and all copies of electrocardiograms performed were obtained. In the absence of precise information from their physicians, the patients were contacted at the end of the study period and questioned about their symptoms and cardiovascular events during the follow-up period. No patient was lost to follow-up.

Statistical analysis: Raw data were stored in a computerized data base. Statistical analysis was performed with the chi-square (or Fisher's exact) test and the Student's *t* test for qualitative and numerical data, respectively, in patients with or without spontaneous documented AF. Then, we sought to determine the predictors of recurrence of AF. The following data were examined: sex, age, accessory pathway location and number, type of tachycardia, presence of structural heart disease, RR interval during AF, point of anterograde accessory pathway block, values of atrial effective and functional refractory periods, AF inducibility before and after ablation study, AF inducibility with 1 extrastimulus versus 2 extrastimuli, and need for electrical shock to interrupt induced AF. Common definitions were used. The accessory pathway refractory period was not included since it was often concealed by the atrial functional refractory period.

RESULTS

Patient characteristics before ablation: Patient characteristics with a history of AF or only reciprocating tachycardia are listed in Table I. Evidence of underlying organic heart disease was present in 13 patients without any difference between the groups: 4 had Ebstein's anomaly, 3 dilated cardiomyopathy, 2 hypertrophic cardiomyopathy, 1 valvular heart disease, 1 coronary artery disease, 1 d-transposition of great vessels, and 1 endomyocardial fibrosis. Thirteen patients had

had 2 and 10 patients ≥ 3 episodes of AF; 52 patients had had a single episode of AF of whom 48 were not receiving antiarrhythmic drugs. One patient had AF persisting for 7 days before referral. Several significant differences appeared in patients with AF (Table I) compared with patients with only reciprocating tachycardia. Patients with AF had shorter cycle lengths leading to anterograde accessory pathway block (252 ± 42 vs 298 ± 83 ms, $p < 0.001$), a greater incidence of atrial vulnerability (89 vs 24%, $p < 0.001$), and there was a greater number of subjects needing electrical cardioversion for induced AF (51 vs 15%, $p < 0.001$). The induction mode of AF (1 vs 2 extrastimuli) was not significantly different in patients in either group who had an atrial vulnerability.

Fourteen patients had a history of cardiac arrest ($n = 2$) or ventricular fibrillation ($n = 12$). Two patients had 2 episodes of ventricular fibrillation. All but 1 patient were not taking oral drugs at the time of sudden death. Ventricular fibrillation was apparently the first symptom of the disease in 4 patients. AF with a rapid ventricular rate was documented just before ventricular fibrillation in 10 patients, whereas in the other 4, AF was presumed to be the initiating mechanism for ventricular fibrillation. Characteristics of these 14 patients were compared with those in the other 61 with only AF and are described in Table II: Patients with ventricular fibrillation had multiple accessory pathways more often (21 vs 7%, $p < 0.01$) and had shorter anterograde conduction parameters.

Follow-up after ablation: During the first week after successful ablation, 5 patients with previous AF had recurrence of arrhythmia at day 3 ($n = 2$) and day 5, 6 and 7 for 1 patient, respectively. There was a single episode in 4 patients which interrupted spontaneously within 4 hours. One patient with hypertrophic cardiomyopathy had nonsustained episodes of atrial tachycardia. After discharge, the mean follow-up period was 35 ± 12 months (range 18 to 76). Ten patients complained of long-lasting palpitations. In 3 patients, the electrocardiogram showed AV nodal reentrant tachycardia (previously diagnosed in all). Seven patients (3 from the ventricular fibrillation group) had recurrent atrial arrhythmia with narrow QRS complexes. All patients had had previous AF (7 of 75 with AF vs 0 of 54 with reciprocating tachycardias, $p = 0.02$). One patient with frequent atrial tachycardia after ablation continued to have recurrences until given a β-blocking drug. The other 6 had the first recurrence of AF at 2, 2, 4, 9, 16 and 24 months, respectively (mean 10 ± 9). There was a single recurrence in 4 and multiple recurrences in 2. A long-term antiarrhythmic drug was given to 4 patients (quinidine to 1, flecainide to 2, sotalol to 1). Only one difference appeared in the characteristics of the 7 patients in whom AF recurred compared with the other 68 without recurrence. Patients with AF recurrence had a greater incidence of atrial vulnerability (6 of 7 vs 37 of 68, $p = 0.004$) after ablation.

In the group with AF, the atrial vulnerability present in 89% of the patients before ablation was observed in only 56% after ablation; this incidence was similar in the short- (53%) and long-term (57%) electrophysiologic results. Therefore, atrial vulnerability disappeared in one third of patients in whom inducibility was initially achieved using an identical stimulation protocol.

TABLE II Characteristics in Patients with Ventricular Fibrillation Compared with Patients with Only Atrial Fibrillation

	Ventricular Fibrillation		
	Absent ($n = 61$)	Present ($n = 14$)	
Men/women	48/13	10/4	NS
Age (years)	36 ± 12	34 ± 14	NS
Presence of cardiopathy (%)	15	7	NS
Accessory pathway location*	13RL 29PS 23LL	3RL 8PS 6LL	NS
Multiple pathways (%)	7	21	0.01
Shortest RR interval (ms)	230 ± 50	172 ± 23	<0.01
Point of anterograde block (ms)	260 ± 41	218 ± 32	<0.01
Right atrial effective refractory period (ms)	213 ± 15	206 ± 19	NS
Right atrial functional refractory period (ms)	238 ± 22	224 ± 21	NS
Inducible AF (%)	90	86	NS
Necessity of electrical shock to interrupt induced AF (%)	42	92	<0.001
Inducibility after ablation (%)	56	55	NS
Follow-up (mos)	35 ± 14	32 ± 15	NS

*Owing to a double accessory pathway in 6 patients, the overall number of accessory pathway location is greater than the patient number.
Abbreviations as in Table I.

DISCUSSION

This study demonstrates that in patients with Wolff-Parkinson-White syndrome and paroxysmal AF, catheter ablation of the accessory pathway significantly reduces the incidence of recurrence of symptomatic atrial arrhythmias.

Atrial fibrillation in Wolff-Parkinson-White syndrome: AF has been reported to occur in up to 32% of patients with Wolff-Parkinson-White syndrome.[18-24] In the present study, 58% of patients had had AF because this arrhythmia was a powerful motive for a curative option in the beginning of our experience. The same reason explains the high prevalence of ventricular fibrillation or cardiac arrest. The only difference between patients with AF and patients with ventricular fibrillation was in the prevalence of multiple accessory pathways and in the ventricular rate possible through the accessory pathway, as shown in other studies.[2,21] Whereas the occurrence of reciprocating tachycardia in patients with accessory pathways is well explained by measurable electrophysiologic properties, the development of AF is less clear. First, several investigators have shown that the initiation of AF could result from degeneration of atrioventricular reciprocating tachycardia.[18-20,22,25] Likewise, patients with documented AF are significantly more likely to have inducible reentrant tachycardia than patients without AF.[21] Second, a relation between clinical or inducible AF and anterograde accessory pathway function has been demonstrated.[18] Patients with AF have significantly shorter RR intervals between 2 preexcited beats during induced AF and shorter accessory pathway refractory periods than patients without AF, but the meaning of this is not well understood. Third, a reentry in the branching network of the accessory pathway has been suggested as a potential mechanism.[26] Fourth, the inducibility of sustained atrial arrhythmia by stimulation techniques is more frequent in patients with than without AF,[16,22-25,27-30] as found in our patients; this suggests a different electrophysiologic substratum between the 2 groups. In most studies, this atrial vulnerability has been assessed by delivering a single atrial extrastimulus, then rapid bursts,[23,24,29,30] whereas our protocol[16] is limited to 1 to 2 extrastimuli. In the present study, use of a single extrastimulus initiated sustained AF in 39% of patients with clinical AF, a figure increasing to 89% with the delivery of double extrastimuli; this sensitivity is similar in patients without the Wolff-Parkinson-White syndrome.[16] The specificity of AF inducibility is less known.[27-30] In asymptomatic patients with Wolff-Parkinson-White syndrome, a value of 85% was found by Gaita et al[28] when using extrastimuli and 69% by Leitch et al[30] when using atrial bursts. The more aggressive protocol probably decreases the clinical significance of AF inducibility.

Low incidence of atrial fibrillation after ablation: Our study shows that with a long follow-up period only a few patients have recurrent AF after successful ablation of the accessory pathway. This is similar to results of surgical ablation, which show a low incidence of atrial vulnerability and AF recurrence: 6% in Sharma's study,[3] 10% in Waspe's study.[4] The previously mentioned factors may explain this low incidence, since the ablation is associated with the disappearance of both reciprocating tachycardia and anterograde accessory pathway function, and a deterioration of branching networks. More surprising is the decreased incidence of atrial "intrinsic" vulnerability, which may also be partly linked to these factors. Even if the significance of atrial vulnerability remains controversial, several investigators have reported that the inability to reinduce AF (under drug therapy) is associated with the clinical control of this arrhythmia in patients either with[23,24] or without[16] Wolff-Parkinson-White syndrome. In the present study, persistence of atrial vulnerability was the only difference found between patients with recurrent or nonrecurrent AF after successful ablation; however, we do not know whether more agressive stimulation would have altered these results. No patient without previous AF presented arrhythmia after discharge, thus suggesting that fulguration is not significantly arrhythmogenic at the atrial level; a longer follow-up period is, however, required to confirm this datum. Results reported here only concern direct-current shock ablation and probably may be applicable to radiofrequency ablation now widely used. Indeed, our experience of radiofrequency include 85 patients within a follow-up period of 1 to 10 months (33 having had AF), and only 2 patients had AF recurrences 4 and 6 months after ablation.

The major limitation to the methods used in this study concerns the assessment of atrial vulnerability. During the preablation study, the reproducibility of AF inducibility was not studied for ethical reasons. The observed ventricular rates were high and thus poorly tolerated hemodynamically, and the duration of induced AF needed an electrical cardioversion in numerous patients. During the postablation period, results of short- and long-term study were combined; nevertheless, we think these different assessment times did not affect the overall results because the incidence of atrial vulnerability was similar in both studies and results were concordant in 92% of patients who underwent both studies. Furthermore, it is possible that a longer follow-up period would show more AF recurrences or that some recurrences were asymptomatic because of a slower ventricular rate. Documented recurrences occurred 1.5 and 24 months after discharge, with a mean of 10 months after ablation, but most (6 of 7, 86%) occurred within the first 18 months after ablation, which was the minimal follow-up period for any patient. This suggests that a longer follow-up period would reveal few additional recurrences. Last, the empirical use of sotalol could be questioned owing to its proarrhythmic effects. Sotalol was chosen because of its combined β-blocking and class III actions, which were thought to be more appropriate in preventing potential arrhythmias originating from the heterogeneous tissue lesions created by fulguration. All patients were discharged after verification that the QT interval was not prolonged and their subsequent supervision was uneventful. Nevertheless, use of sotalol has not been pursued since radiofrequency ablation has replaced fulguration.

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Efficacy of Intravenous Sotalol for Suppressing Inducibility of Supraventricular Tachycardias at Rest and During Isometric Exercise

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The efficacy of intravenous sotalol (1 mg/kg) for suppressing inducibility of supraventricular tachycardias (SVT) with different electrophysiologic mechanisms was studied in 30 consecutive patients referred for an electrophysiologic study because of paroxysmal SVT. Orthodromic SVT using accessory atrioventricular (AV) connection was inducible in 14 patients, AV nodal reentrant SVT in 8, and intraatrial SVT in 8 before administration of sotalol. Isometric handgrip exercise facilitated the inducibility of SVT in 8 patients who were noninducible at rest. After intravenous sotalol, 7 of 14 patients (50%) with orthodromic SVT, 8 of 8 (100%) with AV nodal reentrant SVT, and 8 of 8 (100%) with intraatrial reentrant SVT became noninducible into sustained SVT. Isometric exercise facilitated the inducibility of only 3 nonsustained SVT runs after sotalol infusion, and exercise did not reverse the prolongation of refractory periods of the atrium, AV node, accessory pathway and ventricle caused by sotalol. During a mean follow-up period of 18 ± 7 months, none of the 14 patients who remained noninducible into sustained SVT during the stress test after intravenous sotalol and tolerated long-term oral sotalol therapy had recurrence of symptomatic SVT.

Thus, sotalol is efficacious for suppressing SVT with AV nodal or intraatrial reentrant mechanism, but less efficacious in patients with accessory AV pathway. The β-blocking and cellular antiarrhythmic effects of sotalol are not significantly reversed by exercise.

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Sotalol is a unique antiarrhythmic drug that has both β-blocking and class III antiarrhythmic effects.[1] Its antiarrhythmic efficacy has been documented both in ventricular and supraventricular arrhythmias,[2,3] but its efficacy for suppressing inducibility of various types of reentrant supraventricular tachycardias (SVT) has not been extensively studied. Previous electrophysiologic studies in patients with paroxysmal SVT suggested that pharmacologic β-adrenergic stimulation with epinephrine or isoproterenol, which simulates exercise or other stressful situations, can reverse the effects of antiarrhythmic drugs.[4-8] The purpose of the present study was to determine the efficacy of sotalol for suppressing SVT with different electrophysiologic mechanisms both at rest and during the stress test.

METHODS

Patients: The patient group consisted of 30 patients (21 men and 9 women, mean age 43 ± 14 years) referred for electrophysiologic tests because of symptomatic SVT. The frequency of clinical episodes of symptomatic arrhythmia was occasional (>1/year, but <1/month) in 15 patients, and frequent (>1/month) in 15. Eighteen patients had clinical failure with ≥1 prior antiarrhythmic drug. Eight patients had history of syncopal episodes, 8 had presyncope or dizziness, and 25 had palpitations. One patient had undergone aortic valve replacement because of aortic regurgitation, 2 had coronary artery disease, and 2 had hypertensive heart disease. The other 25 patients had no evidence of structural heart disease. Twelve patients had overt ventricular preexcitation, 2 had short PQ interval (<0.12 second) without preexcitation, and the other 16 had a normal 12-lead electrocardiogram. Patients gave informed consent for the studies.

Electrophysiologic tests: Electrophysiologic tests were performed in a fasting, unsedated state ≥5 half-lives after the discontinuation of all antiarrhythmic drugs. Multiple quadripolar electrode catheters were positioned within the heart through the femoral or antecubital veins, or both, using conventional techniques. Surface electrocardiographic leads V_1 and II, and intracardiac electrograms recorded at the right atrium, His bundle position and right ventricular apex were displayed on an oscilloscope and recorded at a paper speed of 100 mm/second on a Siemens Elema Mingograph 7 recorder. Pacing was performed with a programmable stimulator (Bloom Associates) using stimuli of 2 ms duration and twice the diastolic threshold.

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Incremental atrial pacing, and programmed atrial and ventricular stimulation were performed both at rest and during handgrip exercise in the baseline tests, and after intravenous administration of sotalol.

Handgrip exercise test: Patients performed the isometric exercise test by squeezing the hand dynamometer with a force amounting to 50% of the maximal voluntary contraction, avoiding the Valsalva maneuver during the handgrip. The atrial stimulation protocol began 40 to 50 seconds after the onset of exercise test, which was continued until the longest atrial cycle length with a Wenckebach period in the atrioventricular (AV) node and accessory pathway was observed during incremental pacing, and until atrial and ventricular refractoriness were observed during programmed atrial and ventricular stimulation, respectively. When SVT was induced during the handgrip test, it was terminated by overdrive pacing 30 seconds after its onset or immediately after its repeated induction. If the patient was unable to continue the handgrip test owing to fatigue, the stimulation protocol was continued during another handgrip test performed after a resting period. The resting period lasted 2 to 3 minutes, during which time the sinus cycle length and conduction intervals returned to baseline levels.

Administration of sotalol: The efficacy of intravenous sotalol for suppressing inducibility of SVT was tested in patients without contraindications to β-blockade or clinical failure to sotalol therapy. A total dose of 1 mg/kg of sotalol was administered as an intravenous infusion at a rate of 20 mg/5 minutes. Heart rate, blood pressure and QT interval were measured at 10 minute intervals during the infusion, and the pacing protocol was begun within 5 minutes of its termination. The handgrip test and pacing protocol were performed in the same manner as during the baseline tests.

Measurements: Sinus cycle length, and AV nodal and infranodal conduction times were measured at an atrial paced cycle length of 600 ms. The minimum atrial cycle lengths associated with 1:1 AV or anterograde accessory pathway conduction, or both, were determined by incremental pacing in steps of 10 ms. Refractory periods were measured using 8 beat drive trains at cycle lengths of 600 and 400 ms (only 400 ms during the exercise test), and a single extrastimulus in steps of 10 to 5 ms. Accurate assessment of AV nodal conduction, and refractoriness of the AV node and accessory pathway could not be obtained in all patients, because of preexcitation or shorter AV nodal and accessory pathway refractoriness than atrial or ventricular refractoriness, respectively.

Definitions: Standard criteria were used to determine the mechanisms of orthodromic and AV nodal SVT.[9,10] The criteria used for definition of intraatrial reentry were (1) atrial cycle length between 250 and 600 ms, (2) atrial activation sequence different than that during sinus rhythm, (3) persistence of SVT despite AV block, and (4) initiation and termination of SVT with atrial extrastimuli. SVT was considered noninducible if <5 beats were inducible, nonsustained if there were >5 beats, but the duration was <30 seconds, and sustained if the duration was >30 seconds. The site of antiarrhythmic action of sotalol was considered to be the anterograde limb of the reentrant circuit when echo beats or nonsustained tachycardias terminated in atrial depolarization not followed by ventricular depolarization, and the retrograde limb when ventricular depolarization was not followed by atrial depolarization. If no echo beats were inducible, the site of action was defined by determining the change in refractory period that suppressed the inducibility of SVT. In cases of intraatrial reentry, the site of action was considered to be in the intraatrial circuit when a spontaneous termination of repetitive atrial beats was observed.

Follow-up: Patients who were not inducible into a sustained SVT after administration of intravenous sotalol were discharged receiving the maximal tolerated dose of oral sotalol (160 to 480 mg/day). Follow-up data were obtained by contacting the patient directly.

Statistics: Analysis of variance was used to assess the significances of differences in the electrophysiologic data during the different interventions. Paired *t* test was then used to compare electrophysiologic data at rest and during isometric exercise, and also before and after infusion of sotalol.

RESULTS

Effects of isometric exercise on electrophysiologic data: A summary of the electrophysiologic data measured in the baseline tests and during handgrip exercise before and after administration of sotalol is presented in Table I. Sinus cycle length, AV nodal conduction time and shortest atrial cycle length with 1:1 AV nodal and accessory pathway conduction became shorter during the handgrip test before infusion of sotalol, and the handgrip exercise also significantly shortened the refractory periods of the atrium, AV node, ventricle and accessory pathway.

Electrophysiologic effects of sotalol: Sotalol increased sinus cycle length and prolonged both AV nodal and accessory pathway conduction (Table I). The degree of preexcitation (His to ventricle interval) did not change after sotalol. The atrial and ventricular refractory periods, and retrograde refractory period of the accessory pathway also became longer. Handgrip exercise shortened sinus cycle length and accelerated AV nodal conduction, but did not cause any significant changes in refractory periods after intravenous sotalol.

Characteristics and inducibility of supraventricular tachycardias: The mechanisms of SVT on electrophysiologic study were orthodromic AV reentrant SVT in 14 patients (concealed accessory pathway in 2), AV nodal reentrant SVT in 8, and intraatrial reentrant SVT in 8 (Table II). SVT was inducible in 22 patients at rest, whereas handgrip exercise facilitated SVT induction in 8 (Table II).

Sotalol suppressed the inducibility of 7 of 14 sustained orthodromic SVTs. All 3 nonsustained orthodromic SVTs induced only during the exercise test at baseline study became noninducible after infusion of sotalol.

TABLE I Electrophysiologic Data at Rest and During Handgrip Exercise Before and After Intravenous Sotalol

	Baseline Tests		After Sotalol	
	Rest	Handgrip	Rest	Handgrip
Patients with AVR (n = 14)				
SCL (ms)	795 ± 143	677 ± 102‡	907 ± 150¶	829 ± 117‡
QT interval (ms)	352 ± 24	338 ± 25†	392 ± 23¶	380 ± 20*
AH interval (ms)	45 ± 19	41 ± 15†	50 ± 20	48 ± 16
1:1 AV conduction (ms)**	286 ± 54	258 ± 57†	320 ± 49	302 ± 46*
1:1 AP conduction (ms)	309 ± 59	234 ± 50‡	337 ± 66§	327 ± 59
ERP-A (ms)	226 ± 34	212 ± 33†	253 ± 31‖	252 ± 31
FRP-A (ms)	250 ± 35	237 ± 34†	289 ± 27‖	285 ± 28
ERP-AV (ms)††	272 ± 53	245 ± 70*	321 ± 42§	311 ± 40
ERP-AP (ms)	289 ± 22	232 ± 28*	313 ± 16	312 ± 20
RERP-AP (ms)	272 ± 38	252 ± 32*	295 ± 42§	294 ± 40
ERP-V (ms)	234 ± 25	220 ± 23†	253 ± 22‖	253 ± 24
Patients with AVNR or IAR (n = 16)				
SCL (ms)	866 ± 156	701 ± 105‡	977 ± 125¶	877 ± 120‡
QT interval	382 ± 24	368 ± 25†	410 ± 25¶	402 ± 26*
AH interval	76 ± 31	68 ± 25*	93 ± 50§	86 ± 44*
1:1 AV conduction (ms)	376 ± 63	338 ± 48†	433 ± 66§	399 ± 45*
ERP-A (ms)	230 ± 28	214 ± 25†	267 ± 31‖	267 ± 31
FRP-A (ms)	251 ± 29	236 ± 25†	299 ± 31¶	297 ± 29
ERP-AV (ms)‡‡	311 ± 46	287 ± 40*	369 ± 49§	342 ± 47*
ERP-V (ms)	229 ± 12	215 ± 15†	255 ± 20‖	255 ± 21

*p < 0.05, †p < 0.01, ‡p < 0.001 compared between data at rest and during handgrip exercise.
§p < 0.05, ‖p < 0.01, ¶p < 0.001 compared between data before and after sotalol.
**n = 8; ††n = 7; ‡‡n = 9.
A = atrium; AH = atrium to His. AV = atrioventricular; AVNR = atrioventricular nodal reentry; AVR = atrioventricular reentry; ERP = effective refractory period; FRP = functional refractory period; IAR = intraatrial reentry; RERP = retrograde effective refractory period; RV = right ventricle; SCL = sinus cycle length.

TABLE II Inducibility and Characteristics of Supraventricular Tachycardias Before and After Sotalol

	AVR-SVT (n = 14)		AVNR-SVT (n = 8)		IAR-SVT (n = 8)	
	Rest (n)	Handgrip (n)	Rest (n)	Handgrip (n)	Rest (n)	Handgrip (n)
Before sotalol						
Noninducible	4	0	1	0	3	0
Nonsustained SVT	1	4	1	1	0	2
Sustained SVT	9	10	6	7	5	6
After sotalol						
Noninducible	7	6	7	6	7	7
Nonsustained SVT	0	1	1	2	1	1
Sustained SVT	7	7	0	0	0	0

AVNR-SVT = atrioventricular nodal reentrant SVT; AVR-SVT = atrioventricular reentrant SVT; IAR-SVT = intraatrial reentrant SVT; SVT = supraventricular tachycardia.

TABLE III Antiarrhythmic Mechanisms of Sotalol

	Prolongation of ERP-A	Anterograde Block	Retrograde Block	Block in the Atrial Circuit
Patients with AVR	1	5	2	—
Patients with AVNR	0	3	5	—
Patients with IAR	5	—	—	3

AVNR = atrioventricular nodal reentry; AVR = atrioventricular reentry; ERP-A = effective refractory period of atrium; IAR = intraatrial reentry.

All AV nodal or intraatrial reentrant SVTs became noninducible into a sustained SVT after sotalol. Three nonsustained SVT runs became inducible during the exercise test in patients who were noninducible at rest after infusion of sotalol (Table II).

The sites of the antiarrhythmic action of sotalol in different types of SVT are presented in Table III. Figure 1 displays an example of electrocardiographic recordings in a patient with intraatrial SVT, in whom exercise facilitated and sotalol suppressed the perpetuation of intraatrial reentry circuit.

Follow-up: Twenty-three patients who were not inducible into a sustained SVT after intravenous sotalol either at rest or during handgrip exercise were discharged on oral sotalol (mean daily dose 282 ± 42 mg). Three patients with Wolff-Parkinson-White syndrome who responded to intravenous sotalol were finally treated with radiofrequency ablation of their accessory pathway. Four patients stopped the oral treatment because of side effects. Fourteen patients did not have recurrence of SVT during a mean follow-up of 18 ± 7 months. Two patients who were inducible into nonsustained SVT after intravenous sotalol had palpitations without documented SVT.

DISCUSSION

Electrophysiologic effects of isometric handgrip exercise: Isometric exercise facilitated the induction of SVT in many patients who were noninducible during the baseline test at rest. Facilitation of inducibility is best explained by shortening of atrial refractoriness or by improvement of anterograde conduction over the AV node caused by handgrip exercise and thereby the ability to initiate or perpetuate circuit movement. Handgrip exercise may cause less profound changes in the electrophysiologic properties of the accessory pathway than dynamic exercise or upright posture.[11] However, shortening of the conduction intervals and refractory periods observed during the handgrip stress test was similar in magnitude to that described during pharmacologic β-adrenergic stimulation.[4-8,12] The isometric handgrip exercise test may have some advantages over other stress tests, because it is easy to implement repeatedly during the course of an electrophysiologic study and because it is a physiologic stress test.

Efficacy of sotalol in supraventricular tachycardias: Our results concur with previous studies using intravenous or oral sotalol in that approximately one half of patients with accessory AV pathway became noninducible into SVT after sotalol.[13-16] All patients with AV nodal reentrant SVT responded to sotalol in this study. Rizos et al[17] attained noninducibility in 6 of 8 patients with AV nodal reentrant SVT with intravenous sotalol, and similar results were reported with oral sotalol.[16,18]

There has been less information about the efficacy of antiarrhythmic drugs in patients with intraatrial SVT.[19] Haines and DiMarco[19] reported that this arrhythmia responds poorly to type Ia antiarrhythmic drugs, but is effectively treated with amiodarone. In our study, sotalol was efficacious in all 8 patients with intraatrial reentrant SVT. It seems obvious that class III antiarrhythmic agents that prolong atrial repolarization are highly effective in patients with this arrhythmia.

In agreement with previous findings in patients with accessory AV pathway, the major antiarrhythmic action of sotalol was in the AV node.[18] In AV nodal reentrant SVT, conduction block was observed in both the anterograde slow and retrograde fast pathways after sotalol. SVT became inducible with relatively short atrial coupling intervals (in 3 cases only during the exercise test) in patients with intraatrial SVT, and the antiarrhythmic action of sotalol was either prolongation of atrial refractoriness or block in the intraatrial reentry circuit.

Intravenous sotalol prevented all other electrophysiologic effects of isometric exercise except those on the sinus and AV nodes. The electrophysiologic properties of both the sinus and AV nodes are also dependent on fluctuations in vagal tone,[20] and therefore the effects of exercise on these tissues may not be prevented by β-blockade only. Importantly, exercise did not significantly reverse the class III antiarrhythmic effects of sotalol (i.e., changes in atrial, ventricular and accessory pathway refractoriness). In contrast to these findings, previous studies showed that the antiarrhythmic effects of class I drugs and verapamil are partially reversed by sympathetic stimulation in patients with paroxysmal SVT.[5-8]

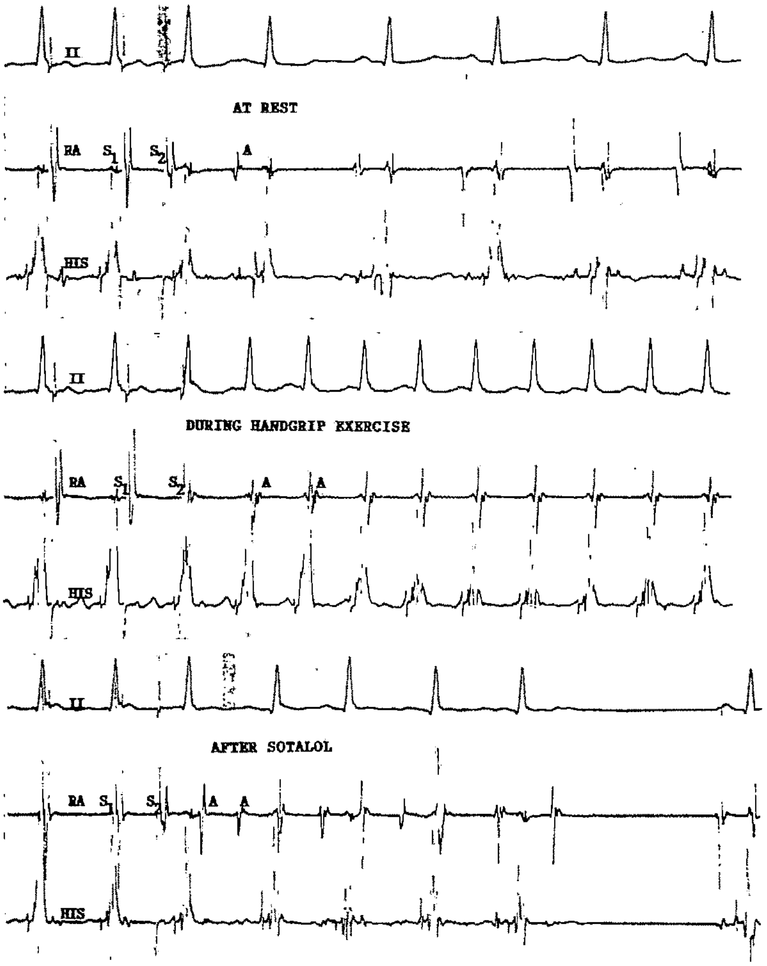

FIGURE 1. Surface and intracardiac electrocardiographic recordings in patient in whom only 1 atrial echo beat was inducible at baseline electrophysiologic study at rest *(top)*. Isometric exercise facilitated inducibility of sustained intraatrial reentrant supraventricular tachycardia *(middle)*. Only short nonsustained supraventricular tachycardia run was inducible during exercise test after intravenous sotalol *(bottom)*. A = atrium; RA = right atrium.

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Conversion of Typical to "Atypical" Atrioventricular Nodal Reentrant Tachycardia After Radiofrequency Catheter Modification of the Atrioventricular Junction

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Typical atrioventricular (AV) nodal reentry tachycardia (AVNRT) is characterized by anterograde activation over a slowly conducting pathway and by retrograde activation through a rapidly conducting pathway. Preliminary reports suggest that radiofrequency catheter modification can eliminate typical AVNRT while preserving anterograde conduction. Radiofrequency catheter modification was used to treat 88 patients with typical AVNRT. After baseline electrophysiologic evaluation, the ablation catheter was positioned proximal and superior to the site of maximal His deflection. Radiofrequency energy was applied until there was significant attenuation of retrograde conduction, and elimination of AVNRT inducibility. Eighty-one patients were successfully treated and form the basis of this report.

A new paroxysmal supraventricular tachycardia with RP > PR interval was induced at electrophysiologic testing after successful ablation in 9 patients (11%). Mean atrial-His activation time was 140 ± 31 ms, and the ventriculoatrial activation time was 170 ± 46 ms. This arrhythmia was induced only with ventricular pacing during isoproterenol infusion and appeared to be mediated by AV nodal reentry. New retrograde dual AV nodal physiology after modification was more frequent in patients with atypical tachycardia than in those without (4 of 9 vs 2 of 72; $p < 0.0001$). Although none of the patients were treated, only 1 of 9 had an episode of spontaneous atypical tachycardia during a mean follow-up of 12 months.

Results of this study confirm that typical AVNRT can be rendered noninducible without the complete destruction of reentrant pathways. Because induction of "atypical" AVNRT was not predictive of spontaneous arrhythmia recurrence, it should not be an indication for additional ablation sessions or long-term drug therapy.

(Am J Cardiol 1992;69:503–508)

Tachycardia due to atrioventricular (AV) nodal reentry (AVNRT) needs 2 nodal or perinodal pathways, differentiated on the basis of their relative conduction times.[1] Typical AVNRT is characterized by anterograde conduction over the "slow" pathway and by retrograde conduction over the "fast" pathway, and accounts for approximately 50% of patients with paroxysmal supraventricular tachycardia. Atypical AVNRT, in which there is retrograde conduction over the slow pathway, and anterograde conduction over the fast pathway, is much less frequent, accounting for <1% of paroxysmal supraventricular tachycardias in most series.[2,3] Preliminary reports suggest that catheter modification of the AV node using radiofrequency energy can eliminate AVNRT while preserving anterograde conduction.[4–6] However, the anatomic substrate for nodal reentry remains incompletely defined. This report describes the occurrence of a new type of tachycardia after successful ablation of typical AVNRT. This tachycardia has the appearance of atypical AVNRT, with a PR interval shorter than the RP interval. The characteristics and clinical significance of this "atypical" tachycardia, and the possible mechanisms by which it occurs are described.

METHODS

Patients and ablative procedure: Between August 1989 and November 1990, 88 patients (29 men and 59 women, mean age 50 ± 18 years) were referred to the University of Michigan Medical Center for treatment of typical AVNRT. This cohort was described in part in previous reports.[4,5] Patients had been symptomatic for a mean of 18 ± 13 years. The ablation procedure was approved by the institutional review board, and all patients gave informed, written consent. All patients underwent a baseline electrophysiologic test to define anterograde and retrograde AV conduction and refractoriness, and to confirm the presence of typical AV nodal reentry tachycardia, using previously described techniques.[7] The following criteria were sought to support the diagnosis of AV nodal reentry: (1) tachycardia induction associated with a critical degree of prolongation of the atrial-His (AH) interval, and (2) atrial activation during tachycardia that was coincident with or closely (<50 ms) followed ventricular activation. Other findings suggestive of AVNRT were the presence of dual AV nodal physiology (discontinuous AV nodal function curves) and tachycardia termination with a premature

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TABLE I Baseline Clinical and Electrophysiologic Characteristics of Patients With and Without "Atypical" AVNRT After Catheter Ablation

	Atypical AVNRT After Ablation	No Atypical AVNRT After Ablation	p Value
No. of pts.	9	72	
Mean age (yr)	52 ± 18	50 ± 19	NS
Men/women	1/8	28/44	NS
Duration of symptoms from AVNRT (yr)	12 ± 10	13 ± 14	NS
Typical AVNRT CL (ms)	314 ± 40	387 ± 77	0.02
AV block CL (ms)	310 ± 60	365 ± 79	NS
VA block CL (ms)	323 ± 79	359 ± 101	NS
Anterograde dual AV nodal physiology	5	51	NS

AV block CL = atrioventricular Wenckebach block cycle length; AVNRT = atrioventricular nodal reentry; NS = not significant; VA block CL = ventriculoatrial Wenckebach block cycle length.

ventricular complex that did not result in activation of the atria. An electrode catheter was not introduced into the coronary sinus, and detailed mapping of the sequence of retrograde activation was not performed. No patient had atypical AV nodal reentry induced before catheter ablation.

The technique for catheter ablation, as previously described,[4] was performed with an electrosurgical unit (Radionics RFG 3-B, Watertown, MA) that delivered a constant, unmodulated sine wave output at 350 kHz. A large-tip (3 or 4 mm in length) electrode catheter was positioned slightly proximal and superior to the site of the maximal His bundle deflection. Recordings from the ablation site typically had an atrial-to-ventricular electrogram ratio ≥1, and a His amplitude <100 μV. A mean of 14 ± 5 W of radiofrequency power was applied between the distal electrode of the ablation catheter and an indifferent skin electrode. Ablation was continued until there was >50% prolongation in the PR interval or ventriculoatrial conduction time, or both, and typical AVNRT could no longer be induced.

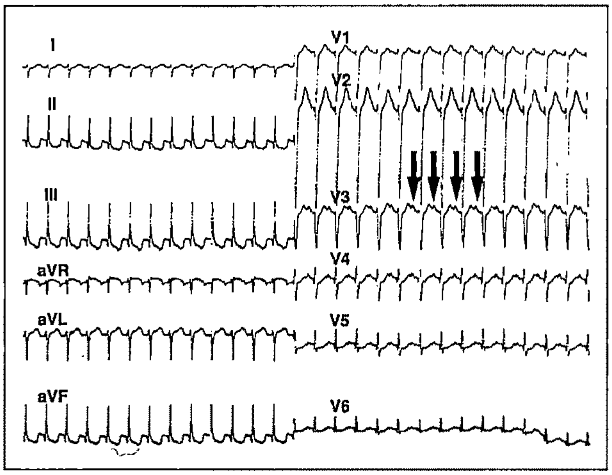

FIGURE 1. Twelve-lead electrocardiogram during atypical atrioventricular nodal reentry induced after radiofrequency catheter ablation. Note short PR interval *(arrows)* and superior P-wave *axis*.

Eighty-one patients had a successful outcome, defined as persistent elimination of typical AVNRT inducibility with preservation of AV conduction, and form the basis of this report. After a successful ablation, electrophysiologic testing was performed before and during isoproterenol infusion at a dose sufficient to increase the heart rate by ≥20%. Complete electrophysiologic testing with evaluation of AV conduction was repeated 2 to 4 days and again at 3 months after the ablation procedure in all patients. At follow-up testing, patients who had a new supraventricular tachycardia characterized by an AH < the His-atrial (HA) interval were considered to have "atypical" tachycardia. Patients with atypical supraventricular tachycardia induced after ablation had complete electrophysiologic evaluations aimed at characterizing the arrhythmia mechanism, including both atrial and ventricular extrastimulus testing during tachycardia.

Data analysis: Results are expressed as mean ± 1 standard deviation. Characteristics of patients with and without atypical tachycardia were compared by analysis of variance and chi-square analysis. The Student's *t* test for paired data was used to compare features of supraventricular tachycardia and AV nodal function before and after ablation. A p value <0.05 was considered significant.

RESULTS

Nine of 81 (11%) patients successfully treated with radiofrequency catheter ablation had new, "atypical" AV nodal reentry induced during the follow-up electrophysiologic study (Figure 1). The arrhythmia was induced immediately after radiofrequency modification in 3 patients and at the early (2 to 4 days) restudy in 4. Atypical tachycardia was induced for the first time at the late (3 months) follow-up test in 3 patients. There were no differences in mean age, sex distribution and duration of symptoms between patients with (group I) and without (group II) atypical AV nodal reentry after ablation (Table I).

Electrophysiologic characteristics of atypical supraventricular tachycardia induced during follow-up evaluation: In all group I patients, atypical supraventricular tachycardia was induced only by ventricular overdrive pacing or programmed stimulation, or both, during isoproterenol infusion (Figure 2). Single atypical echo beats were induced in only 1 patient in the baseline state during ventricular extrastimulation. Initiation of the tachycardia appeared to be dependent on achieving a critical degree of delay in retrograde conduction. In 4 patients, new retrograde dual AV nodal physiology (defined as ≥50 ms increase in ventriculoatrial activation time after 10 ms decrease in the coupling interval of the ventricular extrastimulus) was observed after ablation (Figure 3). In distinct contrast to the baseline findings before ablation, none of these patients had supraventricular tachycardia induced with atrial overdrive pacing or extrastimulation. Characteristics of the arrhythmia are summarized in Table II. Mean tachycardia cycle length was 357 ± 51 ms. Mean AH activation time was 140 ± 31 ms, and ventriculoatrial time was 170 ± 46 ms.

During ventricular pacing, retrograde conduction was decremental and atrial septal activation preceded high right atrial activation in all cases. Tachycardia was reproducibly terminated with ventricular overdrive pacing in 7 of 9 patients. In 1 patient, a ventricular premature stimulus interrupted the tachycardia without subsequent retrograde atrial activation, and in another, spontaneous termination of the arrhythmia after atrial activation was seen.

AV nodal function in group 1 during isoproterenol infusion before and after ablation at the time of induction of atypical AV nodal reentry are compared in Table II. As with the overall population, radiofrequency ablation produced an increase in the AH interval in sinus rhythm from 69 ± 12 to 147 ± 26 ms. Despite the increase in conduction time, there was no change in anterograde AV Wenckebach block cycle length. In contrast, retrograde conduction was significantly attenuated, as reflected by an increase in the ventriculoatrial block cycle length from 257 ± 32 to 344 ± 47 ms (p <0.01). The AH interval during atypical AV nodal reentry was a mean of 67 ms < AH during atrial overdrive pacing at a comparable cycle length of 350 ms.

TABLE II Changes Produced by Ablation in Nine Patients with New "Atypical" AVNRT

	Before Ablation	After Ablation	p Value
Characteristics of Induced AVNRT During Isoproterenol Infusion			
CL (ms)	314 ± 40	357 ± 51	0.05
AH (ms)	237 ± 31	140 ± 31	0.01
VA (ms)	16 ± 9	170 ± 46	0.01
Electrophysiologic Characteristics During Isoproterenol Infusion			
AV block CL (ms)	266 ± 42	257 ± 32	NS
VA block CL (ms)	260 ± 31	344 ± 47	0.01
AH interval in sinus rhythm (ms)	69 ± 12	147 ± 26	0.01
AH interval during AOD (350 ms)	118 ± 62	207 ± 64	0.05

AH = atrio-His interval; AOD = atrial overdrive pacing; CL = cycle length; VA = ventriculoatrial interval; other abbreviations as in Table I.

Comparison of patients with and without atypical atrioventricular nodal reentrant tachycardia: The cycle length of AVNRT induced during the baseline electrophysiologic test was shorter for group I (314 ± 40 ms) than II (387 ± 77 ms; p = 0.02). Anterograde and retrograde AV nodal Wenckebach cycle lengths and the frequency of anterograde dual AV nodal physiology were the same for both groups (Table I).

The number of radiofrequency applications, and the mean voltage, current and duration of each application were similar for the 2 groups (Table III). The amplitudes of the atrial, His and ventricular electrograms at the site resulting in successful ablation of typical AVNRT were also similar for the 2 groups.

Atrioventricular nodal function in patients with and without atypical reentry after successful modification are compared in Table IV. There were no differences in anterograde or retrograde block cycle lengths or effective refractory periods between the 2 groups. Retrograde conduction was present in all 9 patients in group I, and in 37 of 72 in group II (p = 0.0006). There was a trend toward shorter ventriculoatrial conduction times at a paced cycle length of 400 ms in group I than in II (162 ± 10 vs 247 ± 62 ms; p = 0.066). Anterograde dual AV nodal physiology was not seen in any group I patient and was present in 9 group II patients after suc-

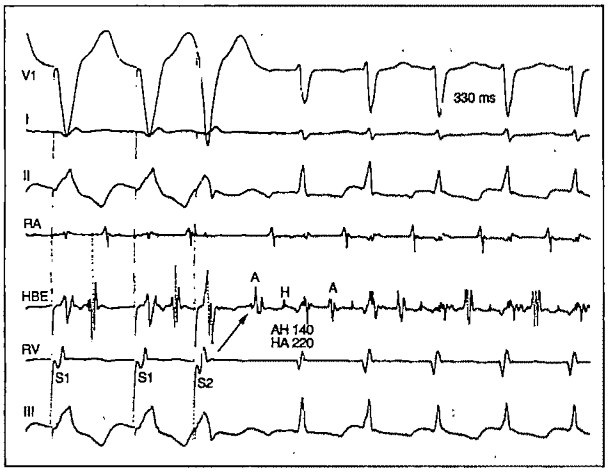

FIGURE 2. Induction of atypical atrioventricular nodal reentry with ventricular extrastimulation. Note initiation of tachycardia with prolongation in ventriculoatrial activation time *(arrow)*. As was characteristic of all group I patients, atrial-His (AH) activation time was less than that of His-atrial (HA). HBE = His bundle electrogram; RA = endocardial electrogram from high right atrium; RV = right ventricular endocardial recording.

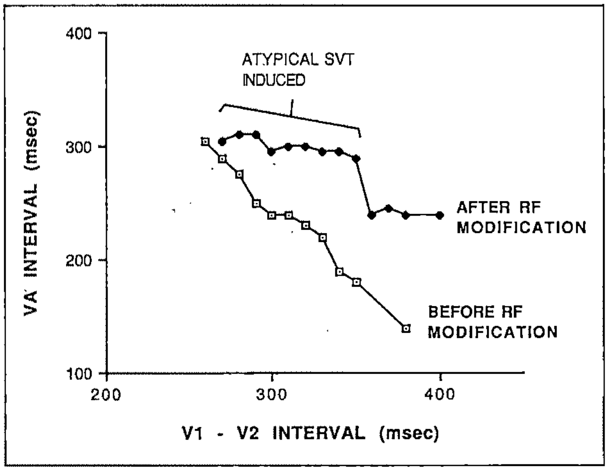

FIGURE 3. Retrograde atrioventricular nodal function curves before and after radiofrequency (RF) modification in patient with atypical supraventricular tachycardia (SVT). Note presence of dual physiology after but not before procedure. Atypical supraventricular tachycardia was consistently induced with coupling intervals associated with conduction over retrograde slow pathway. VA = ventriculoatrial; V1 = ventricular drive train; V2 = ventricular extrastimulus.

TABLE III Ablation Parameters in Patients With and Without "Atypical" AVNRT

	With Atypical AVNRT After Ablation	No Atypical AVNRT After Ablation
Radiofrequency Energy Delivery Parameters		
No. of RF applications	7 ± 4	7 ± 6
Voltage (V)	42 ± 6	45 ± 12
Current (amp)	0.37 ± 0.044	0.35 ± 0.11
Duration (sec)	49 ± 21	52 ± 46
Electrogram Amplitudes at the Effective Site		
Atrial (mV)	2.2 ± .46	1.7 ± 0.7
His (mV)	0.086 ± 0.082	0.066 ± 0.05
Ventricular (mV)	0.92 ± 0.68	0.88 ± 0.70

AVNRT = atrioventricular nodal reentry; RF = radiofrequency energy.

TABLE IV AV Nodal Function 2 to 4 Days After Successful Radiofrequency Modification (during isoproterenol infusion)

	Group I: Atypical AVNRT (n = 9)	Group II: No Atypical AVNRT (n = 72)	p Value
AH interval in sinus rhythm	147 ± 26	136 ± 55	NS
VA interval during ventricular pacing (CL 400 ms)	162 ± 10	247 ± 76	0.066
Maximal VA interval during ventricular overdrive pacing	244 ± 39	252 ± 64	NS
AV block cycle length	257 ± 32	300 ± 76	NS
VA block cycle length	344 ± 47	349 ± 67	NS
AVNERP	220 ± 28	236 ± 43	NS
VA ERP	263 ± 85	269 ± 87	NS
VA conduction	9/9	37/72	0.006
Anterograde dual physiology	0/9	9/72	NS
Retrograde dual physiology	4/9	2/72	0.0001

AV = atrioventricular; AVNERP = atrial ventricular nodal effective refractory period; ERP = effective refractory period; other abbreviations as in Tables I and II.

cessful modification (p = not significant). New retrograde dual physiology occurred in 4 group I and in 2 group II patients (p = 0.0001) after the procedure.

Follow-up of patients with atypical atrioventricular nodal reentrant tachycardia: No patient with atypical AVNRT after ablation received antiarrhythmic therapy or additional ablation sessions. One patient developed a spontaneous, sustained episode of atypical AVNRT 4 weeks after ablation. Therapy with verapamil (240 mg/day) was initiated, but was discontinued after 2 months because of intractable side effects. Repeat electrophysiologic testing at that time showed no retrograde conduction or inducible tachycardia before or during isoproterenol infusion. This patient has been free of arrhythmia recurrence for 13 months without therapy.

The remaining 8 patients have been followed for 12 ± 3 months. None have had symptomatic tachycardias. None of the 6 patients who had atypical AVNRT during their initial hospitalization (either immediately after modification or at the early restudy) had inducible tachycardia at the time of late restudy (3 months). Retrograde conduction was no longer present in 3 of these patients during the late restudy.

DISCUSSION

Main findings: A new paroxysmal supraventricular tachycardia with a long RP interval was induced after successful radiofrequency catheter ablation of typical AVNRT in 9 of 81 (11%) patients. The baseline cycle length of the typical AVNRT was slightly shorter in patients who went on to develop atypical tachycardia than in those who did not. Otherwise, there were no differences in baseline clinical, electrophysiologic or ablation parameters between the 2 groups.

Atypical tachycardia was inducible only by ventricular pacing during isoproterenol infusion and appeared to be mediated by AV nodal reentry. New retrograde dual AV nodal physiology was more frequent in patients with atypical reentry than in those without tachycardia after ablation. Although no patient was treated with antiarrhythmic medications, only 1 of 9 had an episode of spontaneous atypical tachycardia during a mean follow-up of 12 months. Therefore, induction of atypical AV nodal reentry after radiofrequency ablation of typical AVNRT appears to be of little clinical significance.

Comparison with previous studies: Several features of this novel arrhythmia suggest that it was mediated by AV nodal reentry rather than atrial tachycardia or an accessory AV connection. The tachycardia was reproducibly induced with critically timed ventricular extrastimulation, as has been described in patients with spontaneous retrograde dual AV nodal physiology.[8] Termination of the tachycardia with a ventricular premature beat that did not excite the atrium excludes its participation in the reentry circuit. Spontaneous termination after atrial activation also argues against an atrial arrhythmia. There was no evidence of extranodal accessory AV connections, with decremental retrograde atrial activation in all cases.

Haissaguerre et al[9] recently described the follow-up of 42 patients after direct-current shock ablation for AV nodal reentry. Four of 26 patients (15%) undergoing late (4.7 ± 6 months after ablation) electrophysiologic testing had single atypical AV nodal echo beats induced. Apparently none of these patients had sustained tachycardia, but it is not clear how many had repeat testing during isoproterenol infusion.

Observations relating to the site of ablative injury: Several features of patients who developed atypical AVNRT may have implications relevant to the location of ablative injury. The AH interval during atrial pacing was markedly prolonged after ablation. In contrast, the AH interval during atypical AVNRT was relatively short. The AH interval during atrial pacing is the sum of conduction times in the proximal common pathway and the AV node itself, whereas during tachycardia, the AH interval is the difference between these conduction times.[10] Therefore, the conduction delay that was present during atrial pacing was due to slowing proximal to the reentry circuit in the upper common pathway (Figure 4A). This evidence of an upper common pathway strongly suggests that atrial tachycardia was not responsible for the atypical tachycardia induced after ablation.

Anterograde AV nodal block cycle length and refractoriness did not change despite the marked increase in conduction time. A similar pattern was observed in an animal study when ablative injury involved the approaches to the node with relative sparing of the more distal NH region.[11] Some animals in that study had progressive attenuation of AV nodal function in the weeks after ablation, presumably as the result of fibrosis and scar formation. A similar process may account for the loss of retrograde conduction in 4 of 9 patients with atypical AV nodal reentry early after ablation.

Possible mechanisms of atypical reentry after ablation: Possible mechanisms for reentry after ablation are diagrammed in Figure 4. The arrhythmia may represent the original, typical AV nodal reentry with superimposed proximal common pathway delay. Although retrograde conduction in the reentry circuit remains fast, slow conduction in the proximal common pathway would produce a long ventriculoatrial interval. This mechanism seems unlikely because it does not account for the significant slowing of tachycardia rate after ablation and for the inducibility of paroxysmal supraventricular tachycardia by ventricular pacing after ablation but not at baseline.

Ablative injury may have resulted in prolongation of refractoriness in the fast pathway. This could allow selective retrograde block in the fast pathway during ventricular pacing and initiation of atypical AVNRT (retrograde conduction through the slow pathway, and anterograde over the fast pathway). The trend toward a shorter ventriculoatrial time at slower paced rates, and the emergence of retrograde dual AV nodal physiology in 4 of 9 patients is consistent with this hypothesis. The disappearance of retrograde conduction in 4 patients who initially had atypical tachycardia also supports the notion that it was mediated by a damaged fast pathway.

An ablation-induced increase in fast pathway conduction time could account for many of the observations. Although the circuit would be the same as before ablation, retrograde activation would be delayed. The resultant slowing in tachycardia rate might be expected to shorten anterograde conduction time and the AH interval.

Finally, destruction of the fast pathway might unmask a third pathway capable of mediating retrograde conduction, albeit more slowly. Triple pathways have been described,[12,13] and such a pathway may be concealed during the baseline evaluation. McGuire et al[14] recently described a small cohort of patients with 2 types of AV nodal reentry. In addition to typical AV node reentry, they also had a second type of tachycardia with earliest atrial activation near the os of the coronary sinus. As with the patients in the current study, the atypical reentry was characterized by a slower rate, shorter AH intervals and longer ventriculoatrial activation time. They hypothesized that these patients had 2 slow AV nodal pathways located posteriorly, 1 of which was capable of serving at the retrograde limb of a "slow-slow" tachycardia circuit (Figure 3B).

This study is limited by the absence of coronary sinus recordings or retrograde activation times from other sites on the interatrial septum. These data may have clarified whether the atypical reentry was mediated by pathways that were anatomically distinct from those responsible for the initial, typical tachycardia.

Clinical implications: Previous reports of patients treated by either catheter[4-6,16] or operative[17-18] ablation noted control of AVNRT despite persistence of retrograde AV nodal conduction, dual AV nodal physiology and AV nodal echo beats. The results of this study confirm that typical AVNRT can be rendered noninducible without complete destruction of intra- or perinodal reentrant pathways.

Elimination of typical AVNRT was the end point for radiofrequency catheter modification of the AV junction in this series. More than 10% of patients deemed successfully treated had atypical reentry induced after ablation. Sustained tachycardia could only

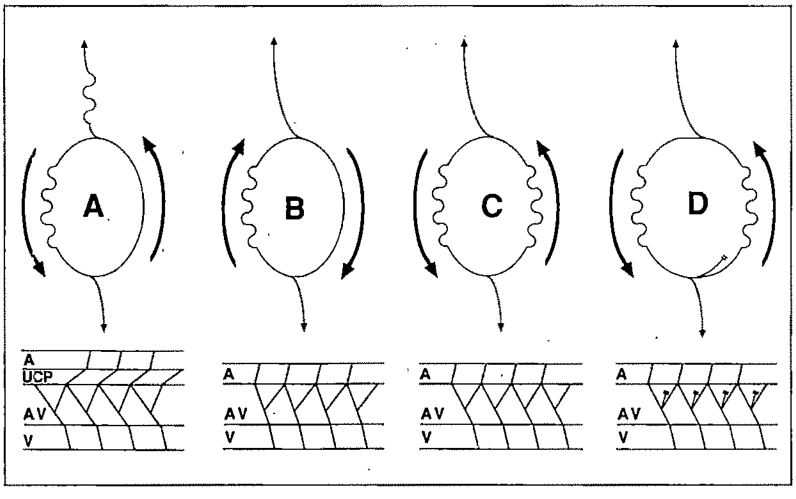

FIGURE 4. Possible mechanisms of atypical atrioventricular (AV) nodal reentry after ablation. *A*, continued typical (up fast–down slow) tachycardia with superimposed ablation-induced upper common pathway (UCP) delay. This proximal delay would prolong retrograde atrial activation time. *B*, ablation-induced increase in fast pathway refractoriness resulting in selective retrograde fast pathway block and initiation of "true atypical" (up slow–down fast) reentry. *C*, slowing in retrograde fast pathway produced by ablative injury causes increased retrograde atrial activation time and slowing of tachycardia rate. Slower rate produces decrease in anterograde ventricular activation time. *D*, ablation interrupts retrograde fast pathway, unmasking a second, slower retrograde pathway. A = atrium; V = ventricle.

be induced during isoproterenol infusion owing to significant attenuation of retrograde conduction. This may account for the low incidence of spontaneous atypical reentry and suggests that induction of this tachycardia should not be an indication for additional ablation sessions or long-term antiarrhythmic therapy.

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Effect of Epinephrine on the Efficacy of the Internal Cardioverter-Defibrillator

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To evaluate the effect of sympathetic activation on the efficacy of the implantable cardioverter-defibrillator (ICD) in converting ventricular tachycardia (VT) or ventricular fibrillation (VF), 32 patients who received an ICD because of life-threatening VT/VF underwent 1 week postimplant ICD testing both before and after infusion of 25 (16 patients) or 50 (16 patients) ng/kg/min of epinephrine for ≥12 minutes. These infusion rates are known to result in plasma epinephrine concentrations comparable to mild-moderate stress. The patients' mean age was 63 ± 10 years; 26 had coronary artery disease, 2 had dilated cardiomyopathy and 4 had no evidence of structural heart disease. VT and VF were induced in 16 patients each by programmed stimulation or alternating current. Among the 16 patients with VT, the first ICD discharge (26 to 30 J) was effective in 15 patients in the baseline state and in all 16 patients during epinephrine infusion. Among patients with VF, the first ICD discharge (26 to 30 J) terminated VF in all patients in the baseline state, compared with 12 of 16 patients during epinephrine infusion ($p < 0.05$). In 4 patients, VF was terminated during epinephrine infusion only by the second or third ICD discharge (30 J). In conclusion, physiologic increases in the plasma epinephrine concentration may increase the number and energy of shocks needed to terminate VF.

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Two recent reports described degeneration of sinus tachycardia to ventricular tachycardia (VT) when shocks from an internal cardioverter-defibrillator (ICD) occurred during physical exercise.[1,2] This suggested that the sympathetic activation that accompanies exercise may have adverse effects on the response to ICD discharges. However, no prior studies have systematically examined the effect of exercise or sympathetic activation on the response to ICD shocks. Therefore, the purpose of this study was to evaluate the influence of sympathetic activation on the efficacy of the ICD in converting VT and ventricular fibrillation (VF). Sympathetic activation was induced with intravenous infusions of epinephrine at doses previously demonstrated to achieve plasma concentrations similar to those observed during mild to moderate physical exercise.[3]

METHODS

Patients: This study consisted of 32 consecutive patients (24 men and 8 women, mean age ± SD 63 ± 10 years) who underwent implantation of an ICD because of life-threatening VT or VF and who underwent testing to evaluate ICD function 1 week later. Twenty-six patients had coronary artery disease, 2 had a dilated cardiomyopathy and 4 had no evidence of structural heart disease. The mean left ventricular ejection fraction as determined by contrast ventriculography was 0.35 ± 0.15.

The clinical presentation was aborted sudden death in 21 patients and sustained VT accompanied by syncope or near-syncope in 11 patients. Among the patients with aborted sudden death, baseline electrophysiologic testing demonstrated inducible sustained monomorphic VT in 8 patients, sustained polymorphic VT in 4 patients and no inducible arrhythmias in 9 patients. Sustained monomorphic VT was inducible in all of the patients in whom the clinical presentation was sustained VT. Patients with inducible monomorphic VT failed serial electropharmacologic testing before ICD implantation.

ICD implantation: The ICD pulse generators and leads were manufactured by Cardiac Pacemakers, Inc. (St. Paul, Minnesota). A median sternotomy approach was used, with rate-sensing screw-in leads positioned on the anterior surface or outflow tract of the right ventricle and defibrillator patch electrodes on the lateral left ventricle and right atrium. Thirty-one patients received a Ventak (model 1550) ICD and 1 patient received a Ventak-P (model 1600).

An external cardioverter-defibrillator (Cardiac Pacemakers, Inc.) was used for intraoperative defibrilla-

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TABLE I Results of the Internal Cardioverter-Defibrillator Conversion Tests

			Baseline					During Epinephrine Infusion					
Pt.	HD	DFT	Rhythm Induced	Duration (s)	No. of Shocks	Effective Energy (J)	First Shock Conversion	Epi	Rhythm Induced	Duration (s)	No. of Shocks	Effective Energy (J)	First Shock Conversion
1	CAD	—	VT	—	1	26	+	25	VT	18	1	26	+
2	CAD	15	VT	17	1	26	+	25	VT	16	1	26	+
3	CAD	20	VT	14	1	30	+	25	VT	18	1	30	+
4	CAD	20	VT	15	1	26	+	25	VT	14	1	26	+
5	CAD	10	VT	20	1	30	+	25	VT	18	1	26	+
6	CAD	10	VT	14	1	26	+	25	VT	15	1	26	+
7	CAD	10	VT	12	1	26	+	25	VT	12	1	26	+
8	CAD	15	VT	19	1	30	+	25	VT	13	1	30	+
9	CAD	15	VT	9	1	26	+	25	VT	21	1	26	+
10	CAD	25	VT	15	1	30	+	25	VT	13	1	30	+
11	CAD	10	VT	13	1	30	+	50	VT	13	1	30	+
12	CAD	10	VT	14	1	26	+	50	VT	14	1	26	+
13	CAD	10	VT	13	1	26	+	50	VT	12	1	26	+
14	CAD	10	VT	13	2	30	—	50	VT	15	1	30	+
15	CAD	15	VT	13	1	26	+	50	VT	12	1	26	+
16	CAD	15	VT	15	1	26	+	50	VF	14	1	26	+
17	CAD	15	VF	15	1	26	+	25	VF	14	1	26	+
18	IDC	15	VF	18	1	30	+	25	VF	16	2	30	–
19	NSHD	15	VF	18	1	26	+	25	VF	23	2	30	–
20	CAD	20	VF	14	1	26	+	25	VT	15	1	26	+
21	CAD	15	VF	11	1	26	+	25	VF	14	1	26	+
22	NSHD	10	VF	14	1	26	+	25	VF	11	1	26	+
23	NSHD	10	VF	11	1	26	+	50	VF	12	1	26	+
24	CAD	5	VF	10	1	30	+	50	VF	10	1	20	+
25	CAD	10	VF	12	1	26	+	50	VF	12	1	26	+
26	NSHD	10	VF	12	1	26	+	50	VF	14	1	26	+
27	CAD	15	VF	12	1	26	+	50	VF	11	3	30	–
28	IDC	20	VF	—	1	30	+	50	VF	14	1	30	+
29	CAD	20	VF	14	1	30	+	50	VF	10	1	30	+
30	CAD	15	VF	11	1	26	+	50	VF	13	1	26	+
31	CAD	10	VF	13	1	26	+	50	VF	13	1	26	+
32	CAD	15	VF	20	1	26	+	50	VF	16	2	30	*–

*The first shock converted ventricular fibrillation to ventricular tachycardia, which was then terminated by a second 30 J shock.

CAD = coronary artery disease; DFT = defibrillation threshold at time of implantation; Duration = time from the induction to the termination in seconds; EPI = infusion rate of epinephrine (ng/kg/min); HD = underlying heart disease; IDC = idiopathic dilated cardiomyopathy; NSHD = no structural heart disease; VF = ventricular fibrillation; VT = ventricular tachycardia.

tion testing. Defibrillation threshold was defined as the minimum energy required to terminate VF. In 4 patients, VF was not inducible and only the minimum energy to convert VT was recorded. To determine the defibrillation threshold, alternating current or rapid pacing was used to induce VF and the defibrillator pulse was delivered after approximately 10 seconds. The defibrillation threshold was 5 J in 1 patient, 10 J in 12 patients, 15 J in 12 patients, 20 J in 5 patients and 25 Joules in 1 patient (Table I).

ICD conversion test: ICD conversion tests were performed 1 week after implantation of the ICD, after informed consent had been obtained. The study protocol was approved by the Human Research Committee of the University of Michigan. With use of a femoral or internal jugular vein, a quadripolar electrode catheter was positioned at the right ventricular apex under fluoroscopic guidance. The surface electrocardiographic leads and intracardiac electrogram were recorded on a Siemens-Elema Mingograf 7 recorder. A programmable stimulator (Bloom Assoc., Ltd.) was used for programmed stimulation using pulses 2 ms in duration at twice the diastolic threshold.

Whenever possible, the ICD shock strength was programmed to be $\geq$10 J greater than the intraoperative defibrillation threshold.[4] A baseline conversion test was then performed after VT or VF was induced with programmed stimulation or alternating current. After the initial conversion test, epinephrine was infused at a rate of 25 and 50 ng/kg/min in 16 patients each. These infusion rates have previously been shown to achieve systemic concentrations comparable with the plasma epinephrine concentrations that occur during mild to moderate exercise.[3] Epinephrine was infused for 12 minutes in order to achieve a steady state, as previously described.[5] Using programmed stimulation or alternating current, VT or VF was then reinduced. An effort was made to induce the same type of arrhythmia as had been induced in the baseline conversion test. During both conversion tests, the type and duration of the induced ventricular arrhythmia, the energy and number of shocks, and the rhythms that occurred after the shocks were recorded. Nonconversion was defined as the persistence of sustained VT or VF after an ICD discharge. Ventricular arrhythmias after conversion were defined as idioventricular rhythm if the rate was <100 beats/min or VT if the rate was ≥100 beats/min.

In 5 patients, the venous plasma concentrations of epinephrine and norepinephrine were measured in the baseline state and 1 minute after the baseline ICD discharge using a single isotope radioenzymatic assay.[6]

Statistical analysis: Statistical analysis was performed using Fisher's exact test or Student's *t* test. A p value <0.05 was considered significant.

RESULTS

Baseline conversion tests (Table I): In the baseline state, before arrhythmia induction, the mean heart rate was 88 ± 19 beats/min. During the baseline ICD conversion test, sustained monomorphic VT, which had a mean cycle length of 294 ± 42 ms, and VF, which had a mean cycle length of 191 ± 16 ms, were induced in 16 patients each. The first ICD shock (26 J in 23 patients and 30 J in 9 patients) was successful in converting 15 of 16 episodes of VT and all episodes of VF to sinus rhythm. One episode of sustained monomorphic VT was converted to sinus rhythm by a second discharge of 30 J after a 26 J discharge had failed.

Conversion tests during epinephrine infusion (Table I): During infusion of epinephrine, before arrhythmia induction, the mean heart rate increased to 93 ± 17 beats/min (not significantly different from baseline). Sustained monomorphic VT, which had a mean cycle length of 287 ± 41 ms, and VF, which had a mean cycle length of 184 ± 20 ms, were again induced in 16 patients each. These mean cycle lengths did not differ significantly from the mean cycle lengths of VT and VF induced in the baseline state. The first ICD discharge was successful in converting 16 of 16 episodes of VT, but was successful in converting only 12 of 16 episodes of VF (p <0.05 compared with baseline). A second or third shock at the same or higher energy was required in 3 patients, and VF converted to sustained VT which required a second shock to terminate in 1 patient. There was no significant difference in the success rate of defibrillation between the 25 and 50 ng/kg/min infusion rates of epinephrine (3/5 VF episodes vs 9/11 VF episodes, respectively). There was no significant difference in the duration of VF (from induction to first shock) between the successful and unsuccessful attempts at defibrillation.

Rhythm after conversion: Immediately after conversion, the mean sinus rate was 77 ± 19 beats during the baseline conversion test and 101 ± 17.5 beats/min during the epinephrine conversion test (p = 0.05). After the successful ICD discharge, there was an idioventricular rhythm in 7 patients (rate 69 ± 11 beats/min lasting for 7.5 ± 2.2 seconds) and nonsustained VT in 5 patients (rate 137 ± 18 beats/min, lasting 7 ± 3.1 seconds) during the baseline test, and there was an idioventricular rhythm in 7 patients (rate 77 ± 13 lasting for 10.2 ± 5 seconds) and nonsustained VT in 10 patients (rate 130 ± 22.5 lasting for 10 ± 7 seconds) during the epinephrine conversion test. There was no significant difference in the incidence, rate or duration of these transient ventricular arrhythmias after shock during baseline or during epinephrine infusion tests.

Plasma epinephrine concentrations: In 5 patients, the plasma concentrations of epinephrine and norepinephrine were measured in the baseline state and immediately after the first ICD discharge. There was a significant increase in plasma epinephrine concentration, from a baseline mean of 78 ± 48 to 150 ± 61 pg/ml after the ICD discharge (p = 0.04). There was no significant change in mean plasma norepinephrine concentration after the ICD discharge (954 ± 854 vs 1,091 ± 929 pg/ml).

DISCUSSION

Effects of sympathetic activation on efficacy of the ICD: This study demonstrates that sympathetic activation may impair the efficacy of the ICD in terminating VF. Infusion of epinephrine at rates that achieve plasma concentrations comparable to those that occur endogenously during exercise resulted in a significant reduction in efficacy of the first ICD discharge in terminating VF, from 100 to 75%. Although VF was always successfully terminated during infusion of epinephrine by a second or third ICD discharge that was of either the same or only slightly greater strength than the first discharge, the failure of the first ICD discharge to defibrillate is consistent with an increase in the energy required to terminate VF. The energy required to defibrillate has been shown to be a continuous probability function instead of a single discrete defibrillation threshold.[7] Therefore, an increase in the energy required to defibrillate is associated with a diminished probability that shocks of a given strength will consistently be effective.

In contrast to VF, all episodes of VT underwent successful cardioversion with the first ICD discharge during the infusion of epinephrine. However, the absence of a discernible effect of epinephrine on the efficacy of the ICD in converting VT does not rule out an effect of epinephrine on the energy required to terminate VT. Because the energy required to terminate VT is generally lower than the energy required to terminate VF, the 26 to 30 J shock delivered by the ICD may have provided a larger margin for successful conversion of VT compared with VF.

Results of prior studies: Experimental studies of the effect of catecholamines on the energy required to defibrillate have had conflicting results. In anesthetized dogs, isoproterenol was found to decrease the defibrillation threshold.[8] In a study performed in pigs, isoproterenol decreased the defibrillation threshold when single pulses were used to defibrillate, but had no effect on the defibrillation threshold when sequential-pulse defibrillation was used.[9] This study also showed that phenylephrine had no effect on the defibrillation threshold. In another study in dogs, epinephrine was found not to have a significant effect on the energy required to defibrillate.[10] However, in this latter study, epinephrine was administered only after VF had been induced,[10] whereas isoproterenol was infused before the induction of VF in the other studies.[8,9]

The discrepancy between the results of the present study and the results of prior experimental studies may be attributable to species differences, differences in the degree of sympathetic activation, or to differences between the effects of epinephrine and isoproterenol. In addition, most subjects in this study had underlying heart disease, whereas the experimental studies used animals that did not have heart disease; it is possible that sympathetic activation has differential effects on the energy required to terminate VF, depending on the presence or absence of heart disease.

Effect of ICD discharges on the plasma epinephrine concentration: Direct-current countershocks of 200 to 300 J delivered to the chest to convert sustained VT have been demonstrated to result in approximately a fivefold increase in the plasma epinephrine concentration.[11] In contrast, the 26 to 30 J ICD shocks in the present study resulted in only a twofold increase in the plasma epinephrine concentration. The greater degree of sympathetic activation associated with the external countershocks may be related to the higher energy of these shocks compared with the ICD shocks.

In a previous study,[12] epinephrine infused in the same dosages as in the present study resulted in mean arterial plasma epinephrine concentrations of 862 ± 226 and 1,374 ± 477 pg/ml. However, arterial plasma concentrations of epinephrine generally are approximately twofold higher than venous plasma concentrations of epinephrine,[13] which were measured in this study. Taking into account the difference between arterial and venous concentrations of epinephrine, the plasma epinephrine concentrations achieved with the 25 and 50 ng/kg/min infusions used in this study, nevertheless, would be expected to be significantly higher than the plasma epinephrine concentration resulting from the discharge of the ICD. Whether the lesser degree of sympathetic activation that occurs after an ICD discharge is sufficient to alter the energy required to defibrillate remains to be determined. If so, it is possible that an ineffective ICD discharge might lower the probability that subsequent ICD discharges will be effective in terminating VF.

Rhythm after conversion: The incidence of transient ventricular arrhythmias after conversion was similar in the baseline state and during epinephrine infusion. These rhythms were generally slow (≤130 beats/min) and short-lasting (≤10 seconds) and therefore not likely to be sensed by the ICD.

Clinical implications: This study has demonstrated that epinephrine infusions that achieve plasma concentrations of epinephrine comparable to those occurring during mild to moderate physical exercise can have a significant effect on the number of ICD shocks needed to terminate VF. Therefore, in patients with a history of VF during exercise, ICD conversion tests ideally should be performed either during exercise or epinephrine infusion. The results of this study also suggest that other types of stress that increase sympathetic tone also may have a deleterious effect on the efficacy of the ICD in terminating VF. This may be a potential explanation for sudden death in patients who have received an ICD. In patients with implantable defibrillators who may be prone to having VF in the setting of sympathetic activation, treatment with a β-adrenergic blocking agent may improve the efficacy of the ICD in terminating VF.

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Clinical and Electrophysiologic Effects of Intravenous Dofetilide (UK-68,798), a New Class III Antiarrhythmic Drug, in Patients with Angina Pectoris

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Dofetilide (UK-68,798) is a new class III antiarrhythmic agent. In animal experiments it selectively prolongs the refractory periods parallel to the action potential duration without any influence on upstroke velocity or conduction parameters. The present double-blind, placebo-controlled study was designed to show the effect of dofetilide on basic electrophysiologic parameters in patients with coronary artery disease. Eighteen patients (aged 31 to 64 years) with symptoms of stable angina pectoris admitted for routine coronary angiography were recruited. They were randomly allocated to receive either placebo or 1 of 2 dose levels of dofetilide intravenously with 6 patients in each group. Paired electrophysiologic variables were compared before and after administration of dofetilide.

Both active dose levels produced significant prolongations ($p < 0.05$) of 10 to 23% in atrial effective refractory period, 6 to 16% in ventricular effective refractory period and 11 to 15% in ventricular functional refractory period. Atrial functional refractory period was prolonged by 14 to 22% at the high-dose level ($p < 0.05$). No effect was observed on conduction parameters (PA, AH, HV, PR or QRS intervals), sinus cycle length or sinus node recovery. The selective prolongation of the refractory periods in both atrium and ventricle, combined with a lack of effect on cardiac conduction parameters, indicates that this drug could be useful in the treatment of both atrial and ventricular reentrant tachyarrhythmias and fibrillation.

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Recent data from the Cardiac Arrhythmia Suppression Trial[1,2] study have highlighted concern regarding the safety and efficacy of class I antiarrhythmic agents. Class I agents inhibit the fast inward sodium channel with a resultant slowing in intracardiac conduction that may predispose to proarrhythmic effects. As a result of the limitations of class I agents, interest in antiarrhythmic drugs with other properties has increased. Class III agents act by prolonging the cardiac action potential resulting in increased refractory periods. Unfortunately the currently available class III drugs have additional activities that confuse the interpretation of their antiarrhythmic profile. Thus, of the clinically available agents, amiodarone has additional class I, II and IV actions,[3] sotalol has β-blocker activity,[4] and bretylium causes catecholamine release followed by prejunctional sympathetic blockade.[5] The absence of specific class III drugs has limited assessment of the therapeutic potential of this group.

Dofetilide (UK-68,798) (Figure 1) is a novel compound derived from the non–β-blocking moiety of the sotalol molecule, which has been shown to produce highly specific class III effects in animal studies.[6,7] Dofetilide has shown no evidence of type I, II or IV activity in animal or early human studies.[6–8]

A previous study of dofetilide in patients with coronary artery disease showed a mean increase in QTc of 81 ms at 4.5 μg/kg.[9] The purpose of the present study was to determine the effect of dofetilide on intracardiac conduction intervals and refractory periods in patients with suspected coronary artery disease.

METHODS

Study group: Eighteen patients aged 31 to 64 years with symptoms of stable angina pectoris admitted for routine coronary angiography were recruited. Women were only recruited if they were postmenopausal or had undergone surgical sterilization. Written informed consent was obtained. The study was approved by the local ethics committee.

Exclusion criteria were: uncontrolled heart failure, unstable angina, recent myocardial infarction (<3 months), previous significant cardiac arrhythmias, QTc >420 ms, systolic blood pressure at rest >200 or <90 mm Hg or diastolic pressure >110 mm Hg. Beta blockers and calcium antagonists were withheld for 2 days and oral nitrates for 12 hours before the study. Sublingual nitrates were allowed throughout the study. All patients underwent a full history and physical exam-

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ination, urinalysis, baseline biochemistry and hematologic assessment before inclusion.

Protocol: After coronary angiography a cannula was inserted in each forearm and flushed with saline solution. Quadripolar electrodes (6Fr) were passed through the femoral veins to the high right atrium and right ventricular apex. A tripolar (7Fr) electrode was placed at the atrioventricular junction to record the His bundle potential. Atrial and ventricular thresholds were determined and the stimulator set to twice threshold with a 2 ms pulse duration. The 3 intracardiac signals and 3 external electrocardiographic channels (I, aVF, V_1) were recorded simultaneously on a Siemens ink jet recorder at 100 mm/s unless specified. All intervals were assessed according to standard definitions.[10] Electrical activity during sinus rhythm was recorded at 250 mm/s for determination of PA, AH and HV intervals. Sinus node recovery times were measured after 90 seconds of continuous atrial pacing at cycle lengths of 600 and 450 ms. Refractory periods were determined using 8-beat drive trains at 600 and 450 ms followed by a single extrastimulus decrementing in 10 ms steps from 450 and 350 ms, respectively. Effective and functional refractory periods were obtained first in the atrium at both cycle lengths and then in the ventricle. Finally, the Wenckebach cycle length was determined. Administration of the study drug was then begun and electrophysiologic study repeated 15 minutes into the maintenance infusion.

The study was conducted in a randomized, double-blind manner to compare 2 doses of dofetilide with placebo. Dofetilide was provided as free base (10 ml × 25 μg/ml) by Pfizer Central Research, Kent, United Kingdom. The dose for each patient was calculated according to the weight in kilograms, and diluted to 25 ml for the loading infusion to be given over 15 minutes and 45 ml for the maintenance infusion to be given over 45 minutes. The diluent contained 50 mg/ml of mannitol and 4 mg/ml of citric acid monohydrate adjusted to pH 3.5 with sodium hydroxide. All doses were prepared immediately before administration by a third party not involved in the rest of the study. Drug administration was terminated if the QTc exceeded 550 ms or if any proarrhythmic or adverse effects were noted.

The 18 patients were divided into 3 groups of 6 and each group received either low-dose dofetilide (3 μg/kg loading + 1.5 μg/kg maintenance), high-dose dofetilide (5 + 2.5 μg/kg) or placebo (diluent only).

Samples for biochemistry and hematology were taken at screening and 24 hours after administration. Hepatitis B serology was checked at screening and repeated if abnormal liver function developed. Drug plasma levels were taken at 0, 5, 10, 15, 20, 30, 40, 50, 60, 70 and 90 minutes after the start of the loading infusion and then at 2, 3, 4, 6, 8, 10 and 24 hours. Samples were centrifuged and the plasma transferred to a plain tube before freezing at −20°C. Plasma levels of dofetilide were measured using a specific radioimmunoassay sensitive to 0.05 ng/ml, with a coefficient of variation of 4% at 1 ng/ml and 25% at 0.1 ng/ml.[11]

A 12-lead electrocardiogram was recorded at screening and at the same time points as plasma samples. A Siemens 740 computerized electrocardiograph was used which automatically calculated the heart rate, PR, QRS, QT and QTc. The QT interval was determined from a composite of all 12 leads using the Glasgow program which has been previously validated.[12] The QTc was calculated using Hodges' linear algorithm as QTc = QT + 1.75 × (heart rate − 60).[13] This algorithm showed a correlation with heart rate closer to zero than the Bazett algorithm in a study of 1,130 normal volunteers.[13] A continuous Holter recording was begun immediately after the electrophysiologic study using a Reynolds Tracker II recorder.

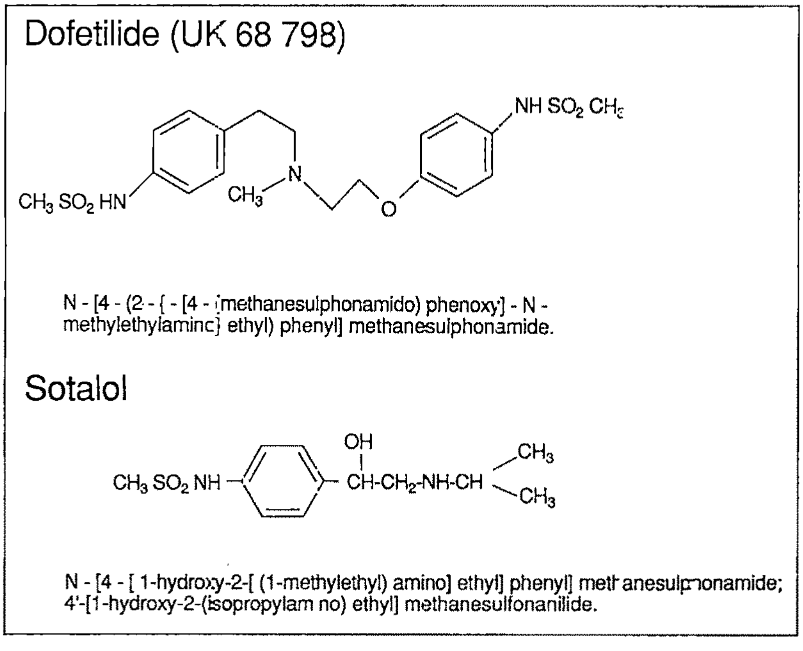
Dofetilide (UK 68 798)
NH SO2 CH3
CH3 SO2 HN
CH3
N
O
N - [4 - (2 - { - [4 - (methanesulphonamido) phenoxy] - N - methylethylamino} ethyl) phenyl] methanesulphonamide.
Sotalol
OH
CH3
CH3 SO2 NH
CH-CH2-NH-CH
CH3
N - [4 - [1-hydroxy-2-[(1-methylethyl) amino] ethyl] phenyl] methanesulphonamide;
4'-[1-hydroxy-2-(isopropylamino) ethyl] methanesulfonanilide.

FIGURE 1. Chemical structures of Dofetilide (UK-68,798) and sotalol.

TABLE I Effects of Dofetilide on Atrial and Ventricular Effective and Functional Refractory Periods (ms)

	Before Dose Mean (SD)	After Dose Mean (SD)	Difference Mean (SD)	%	Variance p Value	No.
AFRP600						
Placebo	274 (23)	276 (23)	2 (10)	1	NS	5
Low dose	268 (27)	293 (26)	25 (18)	9	NS	6
High dose	270 (13)	307 (23)	37 (20)	14	<0.05	6
AERP600						
Placebo	238 (35)	242 (35)	3 (13)	1	NS	6
Low dose	232 (18)	255 (15)	23 (8)	10	<0.05	6
High dose	217 (17)	253 (11)	37 (15)	17	<0.05	6
AFRP450						
Placebo	268 (21)	272 (24)	3 (17)	1	NS	6
Low dose	264 (29)	288 (24)	24 (14)	9	<0.05	5
High dose	262 (19)	320 (24)	58 (11)	22	<0.05*	6
AERP450						
Placebo	222 (23)	228 (26)	7 (8)	3	NS	6
Low dose	223 (20)	248 (24)	25 (11)	11	<0.05	6
High dose	207 (18)	255 (14)	48 (16)	23	<0.05*	6
VFRP600						
Placebo	263 (18)	263 (13)	0 (10)	0	NS	6
Low dose	255 (19)	283 (11)	28 (9)	11	<0.05	6
High dose	265 (17)	300 (23)	35 (13)	13	<0.05	6
VERP600						
Placebo	237 (17)	245 (13)	8 (9)	4	NS	6
Low dose	235 (24)	268 (18)	33 (7)	14	<0.05	6
High dose	238 (18)	275 (25)	37 (14)	15	<0.05	6
VFRP 450						
Placebo	258 (29)	248 (13)	−10 (19)	−4	NS	6
Low dose	242 (19)	268 (16)	27 (14)	11	<0.05	6
High dose	248 (13)	287 (28)	38 (17)	15	<0.05	6
VERP450						
Placebo	242 (37)	232 (11)	−10 (32)	−4	NS	6
Low dose	222 (24)	257 (19)	35 (13)	16	<0.05	6
High dose	225 (19)	262 (23)	37 (13)	16	<0.05	6

*Significant difference between low- and high-dose groups (p <0.05)

AERP = atrial effective refractory period; AFRP = atrial functional refractory period; High dose = 5 μg/kg loading and 2.5 μg/kg maintenance infusions; Low dose = 3 μg/kg loading and 1.5 μg/kg maintenance infusions; NS = not significant (p >0.05); SD = standard deviation; VERP = ventricular effective refractory period; VFRP = ventricular functional refractory period; 450 = 450 ms paced rate; 600 = 600 ms paced rate.

TABLE II Effects of Dofetilide on Intracardiac Conduction Parameters (PA, AH and HV intervals) (ms)

	Before Dose Mean (SD)	After Dose Mean (SD)	Difference Mean (SD)	%	Variance p Value	No.
PA						
Placebo	18 (11)	25 (12)	7 (15)	36	NS	6
Low dose	24 (10)	25 (15)	1 (11)	4	NS	6
High dose	24 (14)	28 (13)	4 (24)	17	NS	6
AH						
Placebo	92 (23)	94 (19)	2 (7)	2	NS	5
Low dose	80 (14)	77 (15)	−3 (8)	−4	NS	6
High dose	84 (24)	93 (33)	9 (16)	11	NS	6
HV						
Placebo	49 (8)	48 (8)	−1 (5)	−2	NS	5
Low dose	52 (4)	49 (9)	−3 (8)	−5	NS	6
High dose	54 (6)	54 (8)	0 (5)	0	NS	6

Abbreviations as in Table I.

Supine blood pressure was recorded at 0, 1, 1.5, 2, 3, 4 and 6 hours after commencement of the loading infusion. Direct recordings through the femoral arterial sheath were used while in the electrophysiology laboratory and paired recordings to 2 mm Hg using a mercury column sphygmomanometer were performed after this.

Statistics: The effects of the 3 dosage regimens on the refractory periods were compared by analysis of variance. The relation of the PR and QRS intervals to plasma levels of dofetilide were assessed by linear regression. A result of $p < 0.05$ was considered significant.

RESULTS

One patient developed atrial fibrillation during the electrophysiology study before receiving the drug, received no study treatment and was not included in analysis. Six patients in each group completed the study. One patient developed atrial fibrillation with aberrancy during the second electrophysiologic study, which converted spontaneously after 15 hours. A second patient was noted on the Holter to have short runs (up to 5 beats) of asymptomatic accelerated idioventricular rhythm (rate 120 beats/min) 15 hours after drug administration. Both these patients were in the low-dose active group. No abnormal rhythms occurred in the high-dose group. We do not believe either event represents a drug-related proarrhythmic effect. No adverse effects were detected or reported by the patients during the study. No significant differences were noted in any of the measured parameters before and after dosing in the placebo group, confirming the reproducibility of the electrophysiologic study. The effects on atrial and ventricular refractory periods are listed in Table I. Effects on the atrioventricular node and His Purkinje system were less well demonstrated because the atrial effective refractory period preceded refractoriness in these tissues, particularly after drug administration. The atrioventricular node effective refractory period was only achieved in both electrophysiologic studies in 8 of the 18 patients, which does not allow statistical analysis. The atrioventricular node functional refractory period was significantly prolonged with the high-dose regimen at both cycle lengths, although the absence of the effective refractory periods make interpretation difficult. No prolongation of His Purkinje conduction was seen in any patient before either the atrial or atrioventricular node effective refractory period occurred. The Wenckebach cycle length was not significantly prolonged and no changes in sinus cycle length or sinus node recovery time were detected at either dose level. No change in systolic or diastolic blood pressure was detected during the study. The PA, AH and HV intervals were not prolonged by either dose level (Table II).

Plasma drug levels remained relatively constant during the period of the electrophysiologic study, averaging 2.9 ± 0.9 ng/ml for the low dose and 4.2 ± 0.9 ng/ml for the high dose (Figure 2). QTc prolongation from baseline averaged 1 ms (0.25%) for placebo, 40 ms (10%) for the low dose and 51 ms (13%) for the high dose during this period. As noted previously, maximal QTc prolongation occurred with the maximal plasma level of dofetilide at the end of the loading dose (Figure

2).[9] This was 50 ± 10 ms at 5.2 ng/ml (range 3.4 to 7.7) for the low dose and 61 ± 12 ms at 9.4 ng/ml (range 4.7 to 13.2) for the high dose. No significant correlation was seen between PR interval or QRS duration and the plasma concentration of dofetilide even at the higher dose (Figures 3 and 4).

DISCUSSION

A previous study[9] demonstrated that dofetilide produced QTc prolongation, which was directly proportional to plasma concentration. These concentrations were 1,000 times less than those required to produce a similar effect with sotalol or amiodarone.[3,4] Nademanee et al[14] demonstrated a 10.8% increase in QTc with 2 to 3 μg/ml of sotalol in patients with ventricular arrhythmias[14] compared with our observation of a 12.7% increase in QTc with dofetilide at a plasma concentration of 4.15 ng/ml. In guinea pig papillary muscle, Tande et al[8] demonstrated similar prolongation of action potential duration with sotalol at 1×10^{-5} M and dofetilide at 1×10^{-8} M. In the present study we have confirmed prolongation of the effective and functional refractory periods in both atrium and ventricle. The percent prolongation was similar in both chambers in this study in contrast to the work of Gwilt et al[6] on anesthetized dogs where atrial refractory periods were prolonged to twice the extent (63%) of ventricular refractory periods (30%) at 100 μg/kg. Their studies showed an increase in action potential duration in ventricular muscle and Purkinje fibers from 13 to 51% and 7 to 81%, respectively, with dofetilide in the concentration range of 5×10^{-9} to 1×10^{-6} M.[6] This is consistent with our findings of a prolongation of refractory periods by 15 to 23% with a plasma concentration of 9.4×10^{-9} M.

Other class III drugs have been shown to act by blockade of potassium channels.[15] Patch clamp studies on isolated guinea pig ventricular myocytes show near abolition of "tail" currents by dofetilide at 5×10^{-8} M, suggesting selective blockade of a time-dependent potassium current with no effect on background currents at negative potentials.[6]

The compound has a half-life of 9.7 ± 2.7 hours, suggesting it should be more rapid in action and easier

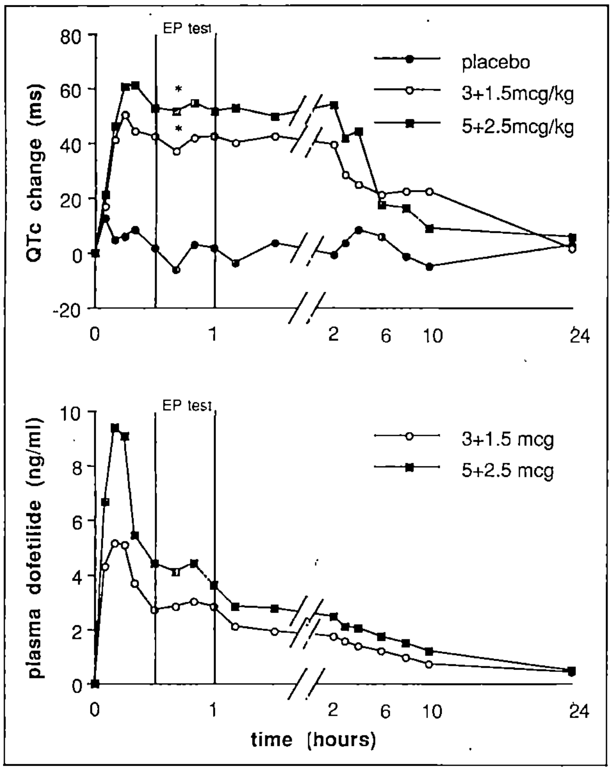

FIGURE 2. Effects of infusion protocols on QTc *(upper panel)* and plasma concentration of dofetilide *(lower panel)*. The infusion protocol achieved stable levels of QTc prolongation between 20 and 60 minutes after the onset of the loading infusion. EP test = electrophysiology test; mcg/kg = micrograms of dofetilide per kilogram body weight; ng/ml = nanograms of dofetilide per milliliter; *significant difference from placebo (p <0.05) from 30 to 60 minutes.

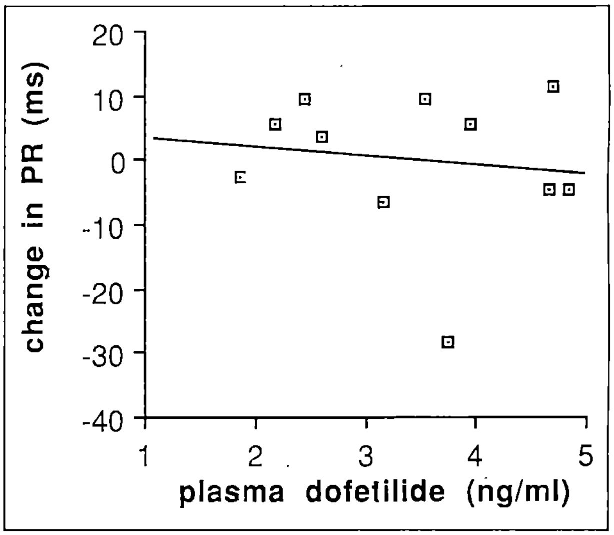

FIGURE 3. Graph of change in PR interval versus plasma concentration of dofetilide at the end of the maintenance infusion (60 minutes). No correlation was demonstrated (r = 0.134, p = not significant). ng/ml = nanograms of dofetilide per milliliter.

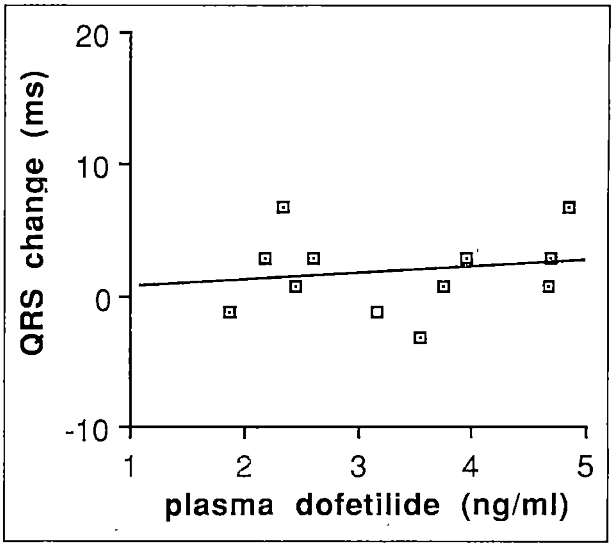

FIGURE 4. Graph of change in QRS duration versus plasma concentration of dofetilide at the end of the maintenance infusion (60 minutes). No correlation was demonstrated (r = 0.164, p = not significant). ng/ml = nanograms of dofetilide per milliliter.

to withdraw than amiodarone which has a terminal half-life of at least 8 to 21 days.[9,16] Dofetilide has been shown to have no effect on action potential amplitude or upstroke velocity in isolated tissue or conduction velocity in dogs, indicating a lack of class I activity.[6] This finding is now supported in humans by both this and previous studies since no effect on heart rate, AH, HV, PA, PR or QRS intervals have been observed.[9,17]

All antiarrhythmic drugs can produce proarrhythmic effects. Torsades de pointes is the most typical arrhythmia reported with class III drugs[18,19] and is thought to arise from bradycardia-dependent early afterdepolarizations arising from the prolonged cardiac action potential. In common with other class III drugs, dofetilide at 10^{-6} M has been shown to produce early afterdepolarizations in 2 of 11 guinea pig papillary muscles paced at 2,000 ms.[8] No such effect was noted in dog ventricle or Purkinje fibers at the same concentration.[6] In this study, plasma levels were much lower and no proarrhythmic effects were observed either on Holter recording or during the electrophysiologic study. Class III drugs are known to show reverse-use dependence, which may limit their efficacy in the presence of a tachycardia.[20] Although we demonstrated no such effects, a previous study of guinea pig papillary muscle with dofetilide at 10^{-6} M showed that prolongation of the cardiac action potential was reduced from 58 to 35% by decreasing the stimulation cycle length from 1000 to 500 ms.[8]

Prolongation of cardiac depolarization with class III drugs has been shown to be associated with a slight positive inotropic effect. Tande and Refsum[21] demonstrated a 12% increase in both contractile force and effective refractory period in rat atria exposed to amiodarone concentrations of 1×10^{-4} M. In a similar preparation d-sotalol produced a 10% increase in contractile force at 1×10^{-5} M.[22] Dofetilide, however, produced significant increases in peak force and maximal rate of force development in guinea pig papillary muscle at concentrations as low as 1×10^{-8} M.[8] The absence of a negative inotropic effect is a particular advantage in antiarrhythmic drug therapy. Recent further analysis of the Cardiac Arrhythmia Suppression Trial[2] has demonstrated that the excess mortality seen in patients receiving class Ic agents resulted not only from sudden deaths but also from an increase in the incidence of cardiac failure and of cardiogenic shock in patients developing reinfarction. Class Ic agents act by blocking sodium channels and may reduce cytosolic calcium levels by sodium calcium exchange.[23] Although studies of dofetilide in patients with impaired left ventricular function will be necessary, the experimental and clinical data so far suggest that dofetilide should be well tolerated hemodynamically.

Prolongation of the cardiac action potential by dofetilide should reduce the excitable gap, thus preventing or terminating reentrant arrhythmias. Potentially, this compound may be useful in the management of reentrant tachyarrhythmias and fibrillation both in atria and ventricles. In this and previous studies, dofetilide has shown an acceptable safety and toleration profile. It also has a pharmacokinetic profile suitable for clinical use. Further evaluation of the therapeutic potential of this drug is therefore warranted.

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SYSTEMIC HYPERTENSION

Safety of Pyridostigmine in Hypertensive Patients Receiving Beta Blockers

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Babeth Rabinowitz, MD, and Jacob Atsmon, MD

In the last decade, pyridostigmine, a quaternary carbamate that reversibly inhibits the enzyme acetylcholinesterase, was proposed for pretreatment of nerve gas (organophosphate) poisoning. The objective of this study was to assess the cardiovascular effects of pyridostigmine in patients treated with β blockers.

Eight hypertensive patients receiving regular treatment with β blockers were randomized in a double-blind crossover study to receive pyridostigmine (30 mg 3 times daily) or placebo for 2 days. Heart rate and blood pressure in the supine and standing positions were recorded every 2 hours during the day, and 24-hour Holter monitoring was performed. In addition, a symptom-limited exercise test was performed, and plasma catecholamine levels were determined at rest and at peak exercise.

Pyridostigmine, as compared with placebo, did not induce any significant effect on heart rate, plasma catecholamine levels or resting blood pressure. Both systolic and diastolic blood pressures increased in accordance with exercise intensity ($p < 0.01$), although a significantly lower diastolic blood pressure was observed when pyridostigmine was used (average decrease 5 mm Hg compared with placebo; $p < 0.01$). No clinical adverse reactions were observed, confirming the relative safety of the combination of low-dose pyridostigmine with β-adrenergic blocking agents.

(Am J Cardiol 1992;69:518–522)

Pyridostigmine, a quaternary carbamate, is a reversible inhibitor of the enzyme acetylcholinesterase. Over the last decade pyridostigmine was proposed for the pretreatment phase of nerve gas (organophosphate) poisoning.[1] Reversible binding of pyridostigmine to acetylcholinesterase protects the enzyme from irreversible inhibition by the nerve agent, thereby potentiating the treatment regimen and enhancing recovery from intoxication.[2]

Although low-doses of pyridostigmine have no significant side effects in healthy subjects,[3] some patients may have untoward reactions due to this agent. These patients may include the elderly, those with conduction disorders, and those concomitantly treated with digitalis, calcium antagonists or β-blocking agents.[4] Considering the frequent use of β-adrenergic blockers, the objective of this study was to assess the cardiovascular effects of pyridostigmine on patients treated with β blockers.

METHODS

Patients: Military personnel treated at an outpatient clinic with β-adrenergic agents for mild to moderate hypertension were selected for inclusion in this study. A screening procedure performed after gradual drug withdrawal included a medical interview, physical examination, blood pressure (measured 3 times on both hands at 5-minute intervals), 12-lead electrocardiogram, chest X-ray, forced expiratory respirometry, Sequential Multiple Analyzer Computer, blood count, urinalysis, 24-hour Holter monitoring and a symptom-limited stress test on bicycle ergometer.

ENTRY CRITERIA: Use of β blockers (propranolol or atenolol) for ≥ 1 year.

EXCLUSION CRITERIA: (1) Acute illness of any kind; (2) chronic disease (e.g., diabetes and pulmonary disease); (3) clinical or electrocardiographic evidence of ischemic or hypertrophic heart diseases; and (4) severe brady- or tachyarrhythmias, or conduction disturbances.

Study protocol: PATIENT MANAGEMENT AND RANDOMIZATION: All patients gave informed consent, approved by the Israel Defense Forces Ethical Committee for Human Research, and were randomized in a double-blind fashion with a counterbalanced crossover to receive pyridostigmine-bromide (Duphar, the Netherlands) or placebo.

The patients were confined for a period of 5 days to a convalescent home where they were under permanent medical supervision and on an identical daily regimen. Figure 1 describes the schedule of the study. The first day served for acclimatization and training on the bicycle ergometer. The study protocol contained 2 phases,

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TABLE I Patient Characteristics and Antihypertensive Therapy

Patient	Age (yr)	BSA (m²)	β Blocker (mg/day)	Additional Drug Therapy
1	25	2.04	Atenolol (50)	0
2	27	2.38	Atenolol (50)	0
3	37	1.99	Atenolol (100)	0
4	38	1.82	Atenolol (50)	0
5	39	1.82	Atenolol (50)	0
6	40	2.05	Atenolol (100)	0
7	41	1.83	Slow-release propranolol (160)	Diuretic, slow K nifedipine
8	42	1.93	Atenolol (50)	Alprazolam imipramine

BSA = body surface area.

TABLE II Supine and Upright Heart Rates, and Blood Pressure at Rest

	Study Drug		β Blocker	
	Placebo	Pyridostigmine	Low Dose	High Dose
Supine HR	68 ± 5	66 ± 5	67 ± 5	67 ± 4
Supine SBP	131 ± 10	129 ± 9	129 ± 7	132 ± 12
Supine DBP	79 ± 8	78 ± 6	77 ± 5	81 ± 10
Upright HR	77 ± 6	76 ± 5	79 ± 5	72 ± 3*
Upright SBP	127 ± 11	126 ± 11	124 ± 9	131 ± 12
Upright DBP	82 ± 8	81 ± 8	80 ± 5	84 ± 11
Orthostatic change in HR	9 ± 5	10 ± 5	12 ± 3	5 ± 3†
Orthostatic change in SBP	−3 ± 4	−4 ± 6	−5 ± 5	−1 ± 4

*p <0.05; †p <0.01.
Data presented as mean ± SD of individual average values (n = 8).
DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg).

each of 2 days' duration. On admission and at the end of each phase, the participants had to fill out a subjective questionnaire addressing their general well-being. At the end of the trial they were asked to guess at which stage they were given pyridostigmine or placebo.

DRUG PROTOCOL: Five doses of either pyridostigmine (30 mg) or placebo were administered every 8 hours during each phase, beginning from 8 A.M. on days 2 and 4 of the trial. The interval from the last dose of the drug in phase I to the first dose in phase II was 16 hours. Patients continued their individual treatment of β blockers concomitantly.

Blood pressure and heart rate were measured in the supine and upright positions in the same hand (determined during the screening) by an automatic blood pressure sphygmomanometer monitor (Lefestat 200). Measurements were obtained at baseline and every 2 hours during the drug therapy, except at night (12 P.M. to 8 A.M.).

EXERCISE TESTS AND HOLTER MONITORING: A symptom-limited exercise test was performed on days 3 and 5 within 2 to 4 hours after the fourth drug dose. This stress test (performed on a Monarch 818 bicycle ergometer) consisted of 25 W increments in load (beginning at 25 W) every 2 minutes.[5] Blood pressure was measured, and a 12-lead electrocardiogram was recorded at baseline, at each work load and during recovery. Holter monitoring (Oxford Medilog 4000) was begun on the evenings of days 2 and 4 for 24 hours. The Holter monitor was removed temporarily during the exercise test. The recordings were reviewed by a cardiologist unaware of the current drug therapy.

PLASMA CATECHOLAMINES: An intravenous route was established before the stress test. Patients were positioned supine at rest for ≥15 minutes before blood samples for catecholamines were obtained. Another sample was obtained immediately after peak exercise. Norepinephrine and epinephrine were determined by high-pressure liquid chromatography.[6]

Statistical analysis: Data are expressed as mean ± standard deviation. We compared the individual average values and also the measurements 2 hours after each drug dose. Three-way analysis of variance with independent effects of pyridostigmine, experimental phase and β-blocker dose was used. The interaction effect between pyridostigmine and β-blocker dosage was also examined. Four-way analysis of variance with the effects of pyridostigmine, phase, β blocker and effort intensity was used for data obtained during exercise testing. Results with $p < 0.05$ were considered statistically significant.

RESULTS

Patients: Twenty-one hypertensive patients treated with β blockers underwent preliminary screening. Nine men fulfilled the entry criteria and volunteered for the study. A 39-year-old patient was excluded from the final analysis owing to severe vasovagal reaction after stress testing while receiving placebo. The remaining 8 subjects (mean age 36 ± 6 years) and their individual treatment are listed in Table I.

Effects on heart rate and blood pressure at rest: Pyridostigmine did not induce any significant effect on heart rate or blood pressure at rest in either the supine or upright position (Table II). Patients who were receiv-

FIGURE 1. Study design. Study protocol consisted of 2 phases of 2 days' duration (days 2 and 3, and 4 and 5). Patients were randomized with counterbalanced crossover to receive 5 doses *(arrow)* of pyridostigmine (30 mg) or placebo. Blood pressure monitoring (every 2 hours), 24-hour Holter recording and symptom-limited exercise testing were performed in each phase.

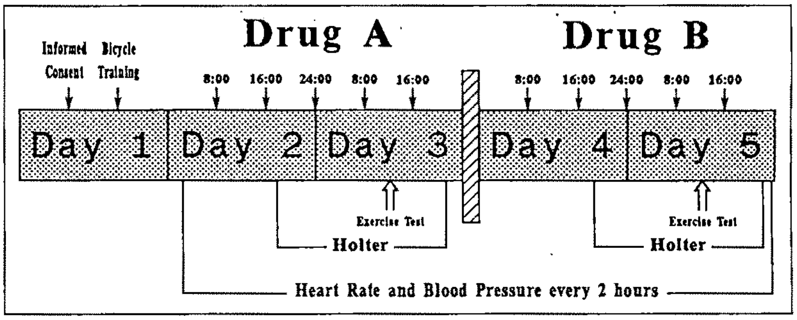

TABLE III Blood Pressure (mm Hg) at Different Exercise Loads During Treatment with Pyridostigmine and β Blockers

Work Load (W)		Study Drug		β Blocker	
		Placebo	Pyridostigmine	Low Dose	High Dose
25	SBP	138 ± 21	131 ± 14	126 ± 12	148 ± 18*
	DBP	88 ± 15	80 ± 10*	80 ± 8	90 ± 18
50	SBP	147 ± 20	140 ± 16	136 ± 14	157 ± 16*
	DBP	87 ± 14	84 ± 9	81 ± 7	93 ± 14
75	SBP	158 ± 23	154 ± 20	146 ± 14	173 ± 19†
	DBP	92 ± 14	87 ± 10†	85 ± 9	96 ± 15
100	SBP	170 ± 22	168 ± 28	159 ± 22	186 ± 21*
	DBP	96 ± 17	94 ± 13	88 ± 10	107 ± 13†
125	SBP	176 ± 20	181 ± 33	165 ± 19	206 ± 20
	DBP	100 ± 13	92 ± 15*	91 ± 14	105 ± 14

*$p < 0.05$; †$p < 0.01$.
Abbreviations as in Table II.

ing a high dose of β blockers (100 mg of atenolol, or 160 mg of propranolol) tended to have a lower heart rate in the upright position compared with that of those who received only 50 mg of atenolol (72 ± 3 vs 79 ± 5 beats/min; $p < 0.05$). The upright position resulted in a significant difference in the magnitude of the increase in heart rate. However, no interaction was found between pyridostigmine and the degree of β blockade.

Holter analysis revealed no difference between pyridostigmine and placebo during regular daily activity. The minimal heart rates (during sleep) were identical (46 ± 4 beats/min [range 42 to 51] with pyridostigmine, and 46 ± 6 [range 40 to 52] with placebo).

Effects on heart rate and blood pressure during exercise: During phase II the patients' exercise capacity was markedly higher than in phase I (maximal load 147 ± 9 vs 125 ± 13 W; $p < 0.01$). This increase in exercise capacity was not related to pyridostigmine. The reasons for termination of exercise were independent of the experimental phase or treatment, and included fatigue in 6 patients, and hypertensive response in 2 (systolic blood pressure >230 mm Hg in 1 patient, and diastolic blood pressure >130 mm Hg in the other).

The effects of pyridostigmine and placebo on heart rate and blood pressure during various work loads are compared in Figures 2 and 3. The 1 parameter significantly affected by pyridostigmine was diastolic blood pressure (Table III). Diastolic blood pressure increased with exercise intensity and decreased with pyridostigmine ($p < 0.01$ for both effects). The effect of pyridostigmine on blood pressure remained consistent during the various stages of the exercise. Thus, no interaction was found between pyridostigmine and the exercise stage. Although systolic and diastolic blood pressures during exercise were higher in patients treated with a higher dose of β blocker ($p < 0.01$; Table III), no interaction was found between pyridostigmine and the degree of β blockade.

Electrocardiography: Neither conduction nor rhythm disturbances were detected on Holter recordings. Pyridostigmine had no effect on PR interval or other parameters of the 12-lead electrocardiogram.

Catecholamines: Plasma catecholamine levels were measured in 7 patients. One patient was excluded owing to emotional lability and concurrent use of tricyclic antidepressants.[7] Norepinephrine levels at rest were 70 ± 19 pg/ml with pyridostigmine, and 68 ± 5 with placebo. Epinephrine levels at rest were <10 pg/ml. Exercise significantly elevated plasma epinephrine (to 59 ± 40 pg/ml with pyridostigmine, and 54 ± 49 with placebo) and norepinephrine (to 326 ± 124 and 295 ± 137 pg/ml, respectively; $p < 0.01$) levels. Thus, pyridostigmine had no significant effect on plasma catecholamines at either rest or peak effort.

Clinical state and subjective assessment: No serious adverse reactions were observed. Patients complained of tiredness, headache, dry mouth, excessive sweating and frequent urination. All these complaints had no correlation with the type of treatment used. In all, 33 complaints were documented with pyridostigmine versus 23 with placebo, and 24 at baseline (p = not significant). When patients were asked at the end of the trial to

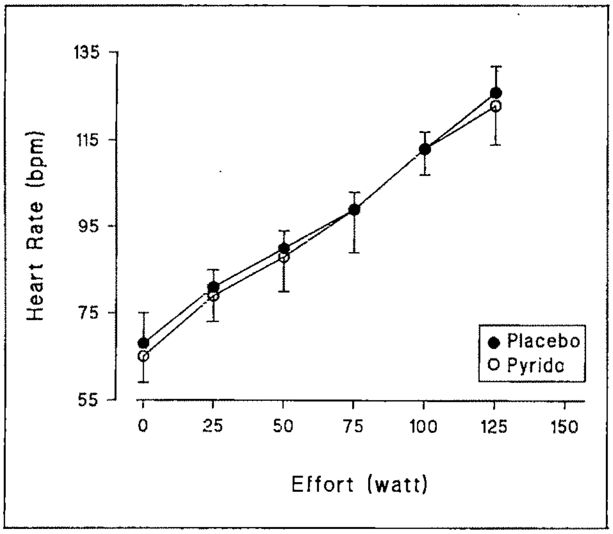

FIGURE 2. Effect of pyridostigmine (Pyrido) on heart rate (mean ± SD) at various exercise levels.

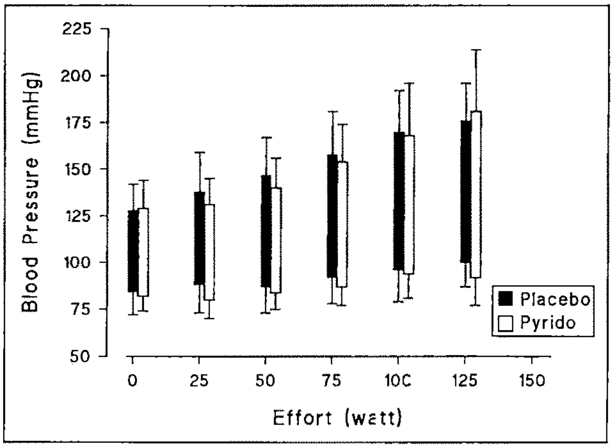

FIGURE 3. Effect of pyridostigmine (Pyrido) on systolic and diastolic blood pressures (mean ± SD) at various exercise levels.

guess their treatment regimen, 3 responded that they were unable to, 2 guessed correctly, and 3 were mistaken.

DISCUSSION

Studies of healthy human subjects showed that the recommended dosage of 90 mg/day of pyridostigmine in 3 separate doses (inducing 20 to 40% inhibition of acetylcholinesterase activity) is devoid of significant physiologic, subjective or functional side effects in healthy people.[3,8-11] However, due to its acetylcholinesterase inhibitory activity, the action of this agent may potentially result in detrimental effects on the cardiac conductive system.[12] Arsura et al[4] described severe cardiac complications in 12 of >1,000 patients with myasthenia gravis treated with pyridostigmine, particularly in elderly ones. During recovery from anesthesia, administration of pyridostigmine was followed by bradycardia or atrioventricular block, if not opposed by atropine.[13] Furthermore, there are reports that the addition of carbamate in patients receiving β blockers may cause life-threatening hemodynamic deterioration, despite concurrent atropine.[14-16] There are few clinical trials in which pyridostigmine was administered to patients with cardiovascular disease.[17,18] To the best of our knowledge, the present report is the first to prospectively evaluate cardiovascular performance after administration of pyridostigmine to patients treated with cardiodepressive drugs.

Exercise in hypertensive patients is associated with an increase in diastolic blood pressure compared with healthy subjects in whom it remains unchanged or decreases.[19] Beta blockade in hypertensive patients is associated with a 20 to 30% reduction in exercise heart rate, a 12 to 22% reduction in systolic blood pressure, and a 17% reduction in diastolic blood pressure compared with those under control conditions.[20]

In our study, a significantly lower diastolic pressure during exercise was observed when pyridostigmine was used (Table III). This finding was not associated with significant changes in heart rate. Hence, it may be attributed to a mild decrease in peripheral vascular resistance that probably resulted from the parasympathomimetic action of pyridostigmine.[21] Considering the increased vascular resistance in essential hypertension and knowing the tendency of β-adrenergic blockers to elevate it further, the decrease in vascular resistance may even prove beneficial to these patients.

Beta-adrenergic blockade was found to elevate plasma catecholamine levels in normal[22] and hypertensive[23,24] subjects, although these changes tend to become attenuated during chronic treatment of hypertension by β blockers.[25] The enhanced sympathetic activity may constitute a compensatory mechanism.[26] In our study, the sympathetic activity was not affected by the addition of pyridostigmine to the β-blockade patients, as proved by the catecholamines. Thus, we did not detect any possible compensatory sympathetic stimulation that could have masked measurable hemodynamic changes. Our results confirm the relative safety of the combination of low-dose pyridostigmine with β blockers. We did not find any detrimental effects on the measured cardiovascular parameters during 2 extreme situations: peak exercise (when the sympathetic limb is maximally excited) and sleep (when the parasympathetic system is dominant).

However, it should be stressed that considering the low overall incidence of clinical untoward cardiac responses in patients treated with pyridostigmine (1%),[4] this study cannot rule out rare, severe drug effects. In addition, long-term safety was not examined. The effects of the administration of pyridostigmine on patients treated with β blockers or other cardiac depressive agents, who also have borderline heart failure or atrioventricular conduction disturbances, are a subject for further investigation.

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Effects of Heart Failure on Baroreflex Control of Sympathetic Neural Activity

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and Allyn L. Mark, MD, with the technical assistance of Joan S. Kempf, LPN

Baroreflex control of heart rate, vascular resistance and norepinephrine is impaired in patients with heart failure, but recent animal studies demonstrate preserved baroreflex control of sympathetic nerve activity in this disorder. Studies were therefore performed to compare baroreflex control of efferent sympathetic nerve activity to muscle in 10 normal subjects (age mean ± SEM 21 ± 1 years) and in 11 patients with moderate to severe heart failure (age 48 ± 5 years, New York Heart Association class II to IV, left ventricular ejection fraction 19 ± 2%, pulmonary capillary wedge pressure 27 ± 2 mm Hg, cardiac index 2.04 ± 0.22 liters/min/m^2). Baroreflex activation was produced by intravenous infusion of phenylephrine (0.5 to 2.0 μg/kg/min) and deactivation by infusion of nitroprusside (0.4 to 2.5 μg/kg/min). During phenylephrine infusion, comparable increases in mean arterial pressure were produced in normal subjects (89 ± 2 to 99 ± 3 mm Hg, $p < 0.01$) and in patients with heart failure (90 ± 2 to 99 ± 3 mm Hg, $p < 0.01$). The patients with heart failure exhibited significantly attenuated ($p < 0.01$ for normal vs heart failure) decreases in heart rate (93 ± 5 to 90 ± 6 beats/min, p = not significant [NS]) compared with normal subjects (67 ± 3 to 58 ± 4 beats/min, $p < 0.01$) and tended to demonstrate attenuated sympathoinhibitory responses to this pressor stimulus. More strikingly, patients with heart failure demonstrated significant impairment of baroreflex responses during nitroprusside-induced baroreceptor deactivation. In normal subjects, nitroprusside produced a decrease in mean arterial (90 ± 2 to 80 ± 3 mm Hg, $p < 0.001$) and right atrial (4 ± 1 to 2 ± 1 mm Hg, $p < 0.01$) pressures with a resultant reflex increase in heart rate (68 ± 3 to 81 ± 4 beats/min, $p < 0.001$) and muscle sympathetic nerve activity (326 ± 74 to 746 ± 147 U/min, $p < 0.01$). In patients with heart failure (n = 10), nitroprusside produced comparable (p = NS for normal vs heart failure) decreases in mean arterial (89 ± 2 to 77 ± 2 mm Hg, $p < 0.001$) and right atrial (6 ± 1 to 1 ± 1 mm Hg, $p < 0.001$) pressures, but did not significantly alter heart rate (91 ± 6 to 97 ± 4 beats/min, p = NS) or sympathetic nerve activity (936 ± 155 to 1179 ± 275 U/min, p = NS). When expressed as percent change in sympathetic nerve activity (U/min) per absolute change in mean arterial pressure (mm Hg) during nitroprusside infusion, the baroreflex sensitivity of the normal subjects (+14.7 ± 2.1% U/mm Hg) was significantly greater than that of patients with heart failure (+1.3 ± 1.7% U/mm Hg, $p < 0.001$). Similarly, when expressed as percent change in sympathetic neural activity (U/min) per absolute decrease in right atrial pressure during nitroprusside infusion, patients with heart failure exhibited a significantly diminished sensitivity (+9.7 ± 4.5%/mm Hg) than did the normal subjects (+59.8 ± 20.5%/mm Hg, $p < 0.05$). Thus, patients with moderate to severe heart failure demonstrate impaired baroreflex control of muscle sympathetic nerve activity and heart rate, which is most pronounced during conditions of baroreceptor deactivation.

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Heart failure is characterized by increased circulating levels of plasma norepinephrine,[1] the magnitude of which appears to be related to the prognosis of these patients.[2] Recent studies from our laboratory demonstrate that increased plasma norepinephrine in patients with heart failure is due to increased central sympathetic neural outflow to muscle, and the magnitude of nerve activity at rest is inversely correlated with the severity of cardiac impairment.[3,4]

The etiology of increased central sympathetic neural outflow in heart failure needs to be fully defined. Studies in experimental models suggest that impairment of cardiopulmonary[5,6] and arterial[7,8] baroreflex mechanisms play an important pathogenic role. In humans, heart failure is associated with impairment of baroreflex control of heart rate, vascular resistance and plasma norepinephrine.[9–16] However, these prior studies in humans have used indirect indexes (e.g., vascular resistance or plasma norepinephrine) to assess the sympathetic efferent limb of baroreflex responses. In contrast to what would be predicted from such studies, recent experimental studies imply preserved baroreflex control of sympathetic nerve activity in heart failure states.[17,18]

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The present studies utilized percutaneous, peroneal microneurography to measure *directly* sympathetic neural responses of normal humans and patients with heart failure to test the hypothesis that clinical heart failure is characterized by impairment of baroreflex-mediated control of efferent sympathetic neural outflow.

METHODS

Human subjects: Twenty-one human subjects were examined: patients with heart failure (n = 11) and normal control subjects (n = 10). Heart failure was defined as any cardiac disorder in which patients had (1) symptoms of dyspnea and exercise intolerance consistent with New York Heart Association functional class ≥II, and (2) presence of reduced cardiac systolic function defined as a left ventricular ejection fraction ≤30% by radionuclide ventriculography. Patients had none of the following: (1) myocardial infarction within 30 days; (2) unstable angina; (3) significant obstructive valvular disease or hypertrophic cardiomyopathy; (4) requirement for prompt treatment with cardiac medications (other than diuretics and nitrates) which could not be discontinued for 4 pharmacologic half-lives before the study; (5) presence of other systemic disorders associated with disturbances in autonomic control of the circulation (e.g., diabetes, systemic hypertension, idiopathic orthostatic hypotension); or (6) required continuance of medications that alter autonomic control mechanisms (antiarrhythmics, adrenergic agonists and antagonists, calcium antagonists, psychotropic agents). Digitalis glycosides were discontinued for ≥7 days before the study and were confirmed by negative findings in the digixon serum assay. All oral medications except for diuretics were withheld for ≥4 half-lives, and diuretics were withheld for ≥12 hours before the study. Diuretic doses were stable in most patients for 2 to 3 days before the study. Intravenous inotropic support being administered to 1 patient with heart failure was discontinued for 3 hours before study. All patients had blood counts, serum electrolyte levels, renal function studies and arterial blood gas determinations performed the morning of study and no patient had hypoxemia, hypercarbia or acidemia. Chest roentgenograms, echocardiograms and electrocardiograms had been obtained within 2 days before the study and all patients were in sinus rhythm.

The normal subjects were untrained and healthy based on medical history and physical examination and were not receiving any medication.

All studies were performed in the supine, postabsorptive state. Informed written consent was obtained before the study, and the protocol was approved by the Human Subjects Review Committee of the University of Iowa.

Hemodynamic measurements in patients with heart failure: On the morning of the study, patients with heart failure had a 7.5Fr flow-directed oximetry thermodilution Swan-Ganz catheter (American Edwards Laboratories, Santa Ana, California) and a 4Fr polyethylene brachial arterial catheter inserted percutaneously under local anesthesia (1% lidocaine, <10 ml). Systemic arterial and right heart pressures were recorded and right-sided oxygen saturation samples excluded an intracardiac left-to-right shunt in all patients. Thermodilution cardiac output was determined using 10-ml iced saline injections (5 measurements) with a SAT-1 Oximeter/Cardiac Output Computer (American Edwards Laboratories). Simultaneous Fick cardiac output was determined by measuring oxygen consumption with a Metabolic Rate Meter (MRM, Waters Instruments, Rochester, Minnesota) and obtaining blood samples for arterial-mixed venous oxygen content difference. During further experimental sessions, pulmonary artery diastolic pressure was used as the measurement of left heart filling pressure because there was excellent correlation ($r = 0.95$, $p < 0.00001$, $n = 11$) between pulmonary artery diastolic pressure and pulmonary capillary wedge pressure. Cardiac output was subsequently measured by thermodilution because of initial excellent correlation ($r = 0.97$, $p < 0.0001$, $n = 11$ patients with heart failure) between thermodilution and Fick methods. Derived hemodynamic parameters were calculated using standard formulas and included systemic and pulmonic vascular resistances (dynes · s · cm^{-5}) and cardiac index (liters/min/m^2).

A direct-writing multichannel physiologic recorder simultaneously recorded phasic arterial, mean (electrical) arterial, right atrial, and pulmonary arterial pressures, electrocardiogram, respiratory activity, and sympathetic nerve activity to muscle. Zero reference point for pressures was defined at the phlebostatic axis in the midaxillary line.

Hemodynamic measurements in normal subjects: In the normal subjects, brachial arterial lines were placed in the manner described for patients with heart failure and cardiac filling pressure was measured as right atrial pressure by inserting an 18.5 gauge polyethylene catheter in an antecubital vein and advancing it to an intrathoracic position for measurement of central venous pressure.

Procedures for perturbing baroreceptors: Steady-state increases in systemic arterial and cardiac filling pressures were used to activate (load) arterial and cardiopulmonary baroreceptors simultaneously. This was achieved by the intravenous infusion of phenylephrine (range 0.5 to 2.0 µg/kg/min), titrated to produce a 10 to 15% increase in mean arterial pressure in normal subjects (n = 10) and in patients with heart failure (n = 10). In 1 patient with heart failure, the peroneal nerve recording site was lost before phenylephrine was infused. The dose of phenylephrine required to achieve comparable hemodynamic results in patients with heart failure (1.37 ± 0.18 µg/kg/min) was not significantly different from that required in normal subjects (1.00 ± 0.11 µg/kg/min, p = not significant [NS]).

Steady-state deactivation (unloading) of arterial and cardiopulmonary baroreceptors was achieved by intravenous administration of sodium nitroprusside (0.4 to 2.5 µg/kg/min), titrated to achieve a 10 to 15% decrease in mean arterial pressure. The dose of nitroprusside required in patients with heart failure (1.03 ± 0.20 µg/kg/min) was also not significantly different from that required in normal subjects (0.96 ± 0.15 µg/

kg/min, p = NS) to achieve comparable hemodynamic results. Nitroprusside was administered to all 10 normal subjects and to 10 of the 11 patients with heart failure (in 1 of the patients with heart failure, the peroneal nerve recording site was lost before nitroprusside was administered).

Microneurographic recording of muscle sympathetic nerve activity: Multiunit recordings of postganglionic skeletal muscle sympathetic nerve activity were recorded from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head in all subjects. This technique has been validated and extensively described in studies from our laboratory[3,4,19-21] and elsewhere.[22-25] Standard criteria for acceptance of a recording were achieved in all subjects.[3,4,19-25] Nerve activity at rest was measured for up to 10 minutes before the study recordings were begun to ensure that a stable baseline of nerve activity had been obtained. Sympathetic bursts were identified by inspection of the mean voltage neurogram. Individual burst frequency was determined as bursts per minute. Total integrated nerve activity was calculated as the total sum of burst amplitudes per minute and expressed as units per minute. Nerve activity was also corrected for heart rate and expressed as bursts per 100 heart beats and units per 100 heart beats.[21] Intragroup comparisons are performed by examining burst frequency and total integrated activity, whereas intergroup comparisons are performed by examining burst frequency. Prior studies in our laboratory determined an intraobserver variability of 5% and an interobserver variability of <10% in this calculation of nerve activity.[24]

Protocol: All subjects and patients were familiarized with the techniques and procedures before the study began. A 20-minute rest period followed the insertion of all catheters and the location of a satisfactory nerve recording site. Control measurements of hemodynamics and sympathetic nerve activity were obtained during a continuous 5-minute period, and cardiac output was determined each minute. After control measurements, vasoactive drugs were infused to activate or deactivate baroreceptors. The order of drug infusion was randomized. Doses were titrated to achieve desired hemodynamic results over 5 to 10 minutes, and then maintained constant during 5-minute recording periods, during which repeated measurements of hemodynamics and nerve activity were recorded during a consecutive 5-minute period. Infusions of the first vasoactive drug were terminated at the completion of recording periods, hemodynamics allowed to return to baseline values over 20 to 30 minutes, and a second 5-minute control period recorded. The alternate vasoactive drug was then infused and titrated as described previously. Once desired hemodynamics were achieved, a second 5-minute recording of hemodynamics and muscle sympathetic nerve activity was obtained.

Statistical analysis: Data presented are the average of the 5-minute values for hemodynamics and sympathetic nerve activity during periods of control and during periods of steady-state vasoactive drug infusion. The mean values for hemodynamics and sympathetic nerve activity variables during respective 5-minute periods before (control) were compared with those during nitroprusside or phenylephrine drug infusion within subject/patient groups by paired *t* test. Intergroup comparisons of control values were performed by unpaired *t* test, as were the absolute and percent changes in variables between 2 different treatment groups. Correlations between Fick and thermodilution cardiac output determinations and between pulmonary capillary wedge and pulmonary artery diastolic pressures were performed by linear regression analysis. Baroreflex sensitivity was calculated as the percent change in total nerve activity (units) divided by the change in mean arterial pressure (mm Hg) or right atrial pressure (mm Hg) during activation (phenylephrine) and deactivation (nitroprusside) of arterial baroreceptors and expressed as the absolute value. Intergroup sensitivity values were compared by unpaired *t* tests during conditions of baroreceptor activation and during conditions of baroreceptor deactivation. Statistical significance was considered as p <0.05. Values are presented in text, table and figures as mean ± SEM.

TABLE I Echocardiographic Characteristics of Normal Subjects and Patients with Heart Failure

Echocardiographic Variable	Normal Subjects (n = 10)	Heart Failure Patients (n = 11)	p Value
Left atrial diameter (cm)	3.5 ± 0.1	4.5 ± 0.2 (n = 9)	<0.001
Left ventricular end-diastolic diameter (cm)	5.3 ± 0.1	7.0 ± 0.3 (n = 9)	<0.001
Left ventricular end-systolic diameter (cm)	3.3 ± 0.1	6.2 ± 0.3 (n = 7)	<0.001
Fractional shortening	0.37 ± 0.02	0.10 ± 0.01 (n = 7)	<0.001
E-point septal shortening (cm)	0.29 ± 0.08 (n = 9)	2.39 ± 0.29 (n = 9)	<0.001

Values are mean ± SEM.

RESULTS

Normal subject and heart failure patient groups: The normal subjects ranged in age from 19 to 29 years (mean 21 ± 1) and had normal cardiac dimensions and function based on echocardiographic criteria (Table I). The patients with heart failure ranged in age from 24 to 74 years and were significantly older than the normal subjects (48 ± 5 years, p <0.001). The etiology of heart failure in these patients included idiopathic cardiomyopathy (n = 8) and ischemic cardiomyopathy (n = 3). The patients were in New York Heart Association class II (n = 3), III (n = 7) and IV (n = 1) at the time of study. The left ventricular ejection fraction (radionuclide ventriculogram) of these patients averaged 19 ± 2% (range 8 to 30), and they had increased cardiac chamber dimensions and reduced indexes of cardiac funtion as assessed by echocardiography (Table I). The resting hemodynamic characteristics of the patients with heart failure are summarized in Table II and were remark-

TABLE II Resting Hemodynamic Characteristics of Patients with Heart Failure (n = 11)

Hemodynamic Variable	Mean ± SEM	Range
Systolic arterial pressure (mm Hg)	116 ± 5	88–143
Diastolic arterial pressure (mm Hg)	77 ± 2	67–91
Mean arterial pressure (mm Hg)	89 ± 4	73–100
Heart rate (beats/min)	93 ± 6	62–120
Right atrial pressure (mm Hg)	10 ± 1	6–16
Pulmonary arterial systolic pressure (mm Hg)	51 ± 5	30–87
Pulmonary arterial diastolic pressure (mm Hg)	29 ± 3	15–38
Pulmonary arterial mean pressure (mm Hg)	36 ± 3	21–47
Pulmonary capillary wedge pressure (mm Hg)	27 ± 3	11–37
Thermodilution cardiac index (liters/min/m^2)	2.04 ± 0.22	1.10–2.97
Fick cardiac index (liters/min/m^2)	2.18 ± 0.18	1.48–3.15
Arterial mixed venous oxygen content difference (vol%)	7.14 ± 0.63	4.51–10.30
Systemic vascular resistance (dynes · s · cm^{-5})	1,784 ± 205	1,019–3,141
Pulmonic vascular resistance (dynes · s · cm^{-5})	217 ± 44	81–536

able for relative tachycardia, increased ventricular filling pressures, decreased cardiac index, widened arterial mixed-venous oxygen content difference, and both systemic and pulmonic vasoconstriction.

Responses of normal subjects and patients with heart failure to baroreceptor activation (phenylephrine infusion): Table III and Figure 1 summarize the hemodynamic and sympathetic neural responses of normal subjects and patients with heart failure to baroreceptor activation produced by intravenous phenylephrine. Phenylephrine produced comparable increases in arterial systolic (normal subjects, +6 ± 1%; patients with heart failure, +9 ± 2%; p = NS), diastolic (normal, +9 ± 1%; heart failure, +10 ± 1%; p = NS), pulse (normal, +2 ± 3%; heart failure, +5 ± 3%; p = NS), and mean (normal, +11 ± 1%; heart failure, +10 ± 1%; p = NS) pressures in both groups. Similarly, phenylephrine produced comparable increases in right atrial pressures (normal, +81 ± 14%; heart failure, +62 ± 9%; p = NS) in both groups.

Despite producing similar increases in arterial pressures, phenylephrine infusion produced differing reflex heart rate responses in the 2 groups. Phenylephrine infusion resulted in significantly less bradycardia in patients with heart failure than in normal control subjects, with the heart failure patients having an attenuated decrease in heart rate (normal, −14 ± 3%; heart failure, −4 ± 2%; p <0.01) in response to the increase in blood pressure.

The sympathoinhibitory responses to baroreceptor activation also tended to be attenuated in patients with

TABLE III Responses of Normal Subjects and Patients with Heart Failure to Baroreceptor Activation (phenylephrine)

	Normal Subjects (n = 10)		Heart Failure Patients (n = 10)	
Parameter	Control	Phenylephrine	Control	Phenylephrine
Systolic arterial pressure (mm Hg)	130 ± 3	138 ± 3*	121 ± 3	132 ± 5*
Diastolic arterial pressure (mm Hg)	69 ± 2	76 ± 3*	73 ± 2	81 ± 3*
Mean arterial pressure (mm Hg)	89 ± 2	99 ± 3*	90 ± 2	99 ± 3*
Pulse pressure (mm Hg)	61 ± 3	62 ± 3	47 ± 3†	51 ± 5
Pulmonary arterial systolic pressure (mm Hg)	—	—	55 ± 6	64 ± 6*
Pulmonary arterial diastolic pressure (mm Hg)	—	—	26 ± 3	32 ± 3*
Pulmonary arterial mean pressure (mm Hg)	—	—	37 ± 4	43 ± 4*
Right atrial pressure (mm Hg)	4.0 ± 0.7	6.7 ± 0.9*	7.2 ± 1.2†	10.8 ± 1.2*
Heart rate (beats/min)	67 ± 3	58 ± 4*	93 ± 5†	90 ± 6 (p = 0.07)
Thermodilution cardiac output (liters/min)	—	—	4.02 ± 0.41	3.57 ± 0.43*
Systemic vascular resistance (dynes · s · cm^{-5})	—	—	1,822 ± 166	2,227 ± 220*
Pulmonic vascular resistance (dynes · s · cm^{-5})	—	—	243 ± 49	310 ± 58*
Muscle sympathetic nerve activity				
Bursts/min	32 ± 5	17 ± 5*	61 ± 8†	47 ± 10*
U/min	384 ± 85	172 ± 59*	1,014 ± 151	736 ± 173 (p = 0.06)
Bursts/100 heart beats	46 ± 5	28 ± 7*	65 ± 7†	49 ± 9*
U/100 heart beats	538 ± 93	265 ± 79*	1,088 ± 174	759 ± 169 (p = 0.08)

Values are mean ± SEM.
*p ≤ 0.01 vs control; †p < 0.05 normal control vs heart failure control.

heart failure when expressed as change in sympathetic burst frequency (normal, −51 ± 8%; heart failure, −30 ± 9%; p = 0.10) or total integrated sympathetic activity (normal, −61 ± 8%; heart failure, −36 ± 12%, p = 0.10) but these differences were not statistically significant. When changes in sympathetic activity were corrected for accompanying changes in heart rate, there were no differences between the 2 groups. Phenylephrine infusion produced comparable attentuation of sympathetic burst frequency corrected for accompanying changes in heart rate (normal, −43 ± 9%; heart failure, −28 ± 9%; p = NS) and total sympathetic activity corrected for heart rate (normal, −54 ± 9%; heart failure, −34 ± 12%; p = NS).

Calculation of baroreflex sympathetic sensitivity (change total integrated muscle sympathetic nerve activity [%] divided by absolute change in mean arterial pressure [mm Hg]) during baroreceptor activation revealed no difference between the normal subjects (−6.3 ± 0.6%/mm Hg) and patients with heart failure (−4.7 ± 2.2%/mm Hg, p = NS). However, when the sensitivity was derived as the change in total integrated nerve activity [%] divided by the absolute change in right atrial pressure [mm Hg] during phenylephrine infusion, there was a significant difference between the normal subjects (−28.1 ± 5.7%/mm Hg) and patients with heart failure (−10.9 ± 3.7%/mm Hg, p <0.05).

Responses of normal subjects and patients with heart failure to baroreceptor deactivation (nitroprusside infusion): Table IV and Figure 1 summarize the hemodynamic and sympathetic neural responses of normal subjects and patients with heart failure to baroreceptor deactivation produced by intravenous nitroprusside. Nitroprusside produced comparable decreases in arterial systolic (normal subjects, −11 ± 1%; heart failure patients, −12 ± 2%; p = NS), diastolic (normal, −10 ± 1%; heart failure, −15 ± 2%; p = 0.07), pulse (normal, −11 ± 3%; heart failure, −4 ± 6%; p = NS) and mean (normal, −11 ± 1%; heart failure, −14 ± 2%; p = NS) pressures in the 2 groups. Similarly, nitroprusside produced comparable decreases in right atrial pressures (normal, −80 ± 29%; heart failure, −94 ± 15%; p = NS) in both groups.

In response to similar alterations in arterial pressure parameters, infusion of nitroprusside tended to elicit attenuated heart rate responses in patients with heart failure (+8.6 ± 4.7%) than in normal subjects (+19.6 ± 3.9%), but these differences did not achieve statistical significance (p = 0.09).

A significant difference in sympathoexcitatory neural responses during nitroprusside infusion was noted between normal subjects and patients with heart failure. Despite similar or somewhat greater reductions in arterial and cardiac filling pressures in the heart failure pa-

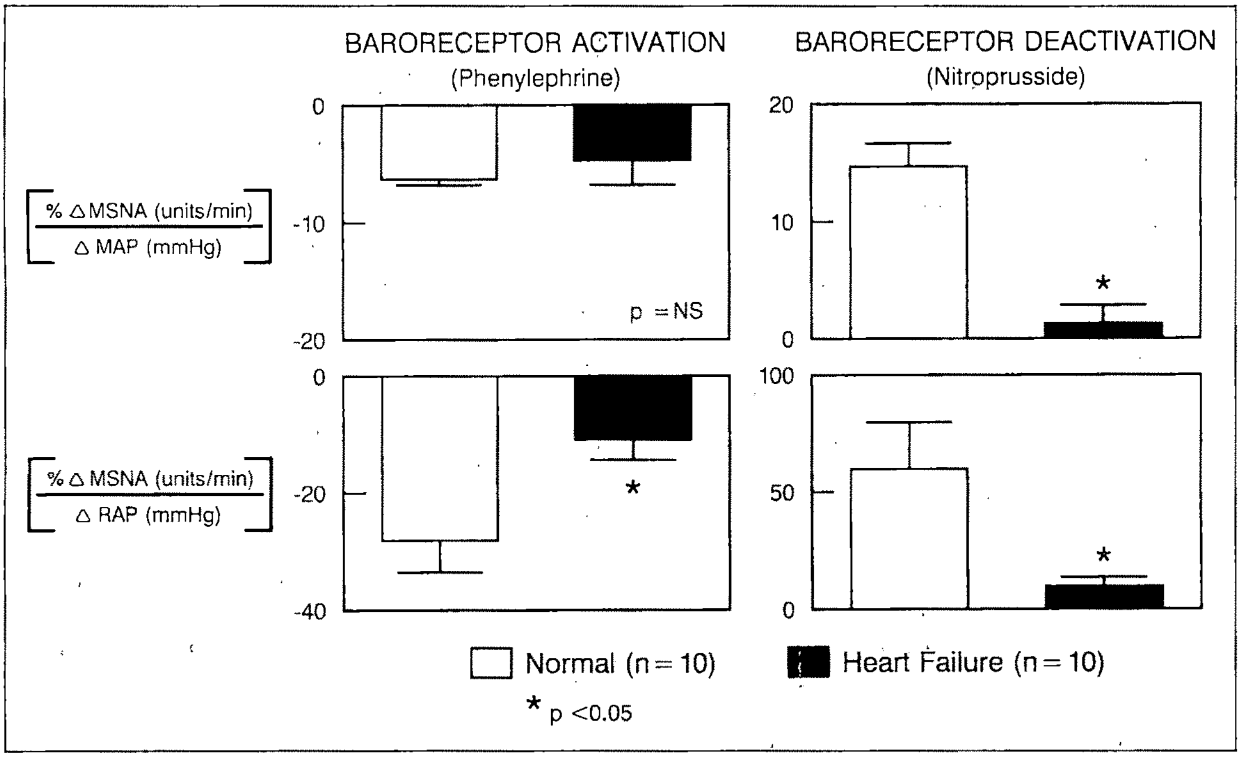

FIGURE 1. Comparison of baroreflex sympathetic sensitivity of normal subjects and patients with heart failure in response to baroreceptor activation (intravenous phenylephrine, *left panels*) and deactivation (intravenous nitroprusside, *right panels*). Patients with heart failure appeared to have an attenuation of sympathoinhibitory responses to baroreceptor activation when expressed as percent decrease in total integrated muscle sympathetic nerve activity (MSNA) per absolute increase in right atrial pressure (RAP). More strikingly, patients with heart failure demonstrated marked attenuation of sympathoexcitatory responses to baroreceptor deactivation when expressed as percent increase in total integrated MSNA per absolute decrease in mean arterial pressure (MAP, *upper panel*) or right atrial pressure (*lower panel*). Values are mean ± SEM for both groups (n = 10). NS = not significant; *p <0.05 heart failure versus normal.

TABLE IV Responses of Normal Subjects and Patients with Heart Failure to Baroreceptor Deactivation (nitroprusside)

Parameters	Normal Subjects (n = 10)		Heart Failure Patients (n = 10)	
	Control	Nitroprusside	Control	Nitroprusside
Systolic arterial pressure (mm Hg)	134 ± 3	120 ± 4*	118 ± 3†	104 ± 3*
Diastolic arterial pressure (mm Hg)	69 ± 2	62 ± 2*	73 ± 2	62 ± 2*
Mean arterial pressure (mm Hg)	90 ± 2	80 ± 3*	89 ± 2	77 ± 2*
Pulse pressure (mm Hg)	65 ± 3	58 ± 3*	45 ± 3†	42 ± 2
Pulmonary arterial systolic pressure (mm Hg)	—	—	49 ± 5	29 ± 4*
Pulmonary arterial diastolic pressure (mm Hg)	—	—	24 ± 3	13 ± 2*
Pulmonary arterial mean pressure (mm Hg)	—	—	33 ± 4	20 ± 3*
Right atrial pressure (mm Hg)	3.9 ± 0.8	1.7 ± 0.6*	5.8 ± 1.0	1.0 ± 0.6*
Heart rate (beats/min)	68 ± 3	81 ± 4*	91 ± 6†	97 ± 4
Thermodilution cardiac output (liters/min)	—	—	4.21 ± 0.45	5.49 ± 0.51*
Systemic vascular resistance (dynes · s · cm^{-5})	—	—	1,769 ± 182	1,181 ± 92*
Pulmonic vascular resistance (dynes · s · cm^{-5})	—	—	213 ± 46	106 ± 23*
Muscle sympathetic nerve activity				
Bursts/min	28 ± 4	49 ± 5*	63 ± 8†	70 ± 6
U/min	326 ± 74	746 ± 147*	936 ± 155	1,179 ± 275
Bursts/100 heart beats	39 ± 4	59 ± 4*	68 ± 6	73 ± 6
U/100 heart beats	452 ± 86	877 ± 151*	1,025 ± 190	1,245 ± 319

Values are mean ± SEM.
*p <0.01 vs control; †p <0.01 normal control vs heart failure control.

tients, normal subjects exhibited significantly greater increases in sympathetic nerve burst frequency than did heart failure patients (normal, +93 ± 20%; heart failure, +21 ± 12%; p <0.01). This difference in sympathetic excitation persisted when expressed as change in total integrated sympathetic activity (normal, +148 ± 31%; heart failure, +33 ± 17%; p <0.01), burst frequency corrected for accompanying changes in heart rate (normal, +60 ± 13%; heart failure, +11 ± 9%; p <0.01), and total activity corrected for accompanying changes in heart rate (normal, +106 ± 21%; heart failure, +21 ± 14%; p <0.01).

Calculation of a baroreflex sympathetic sensitivity (change total integrated nerve activity [%] divided by absolute change in mean arterial pressure [mm Hg]) during baroreceptor deactivation revealed that heart failure patients had significantly diminished sensitivity (+1.3 ± 1.7%/mm Hg) compared with the normal sub-

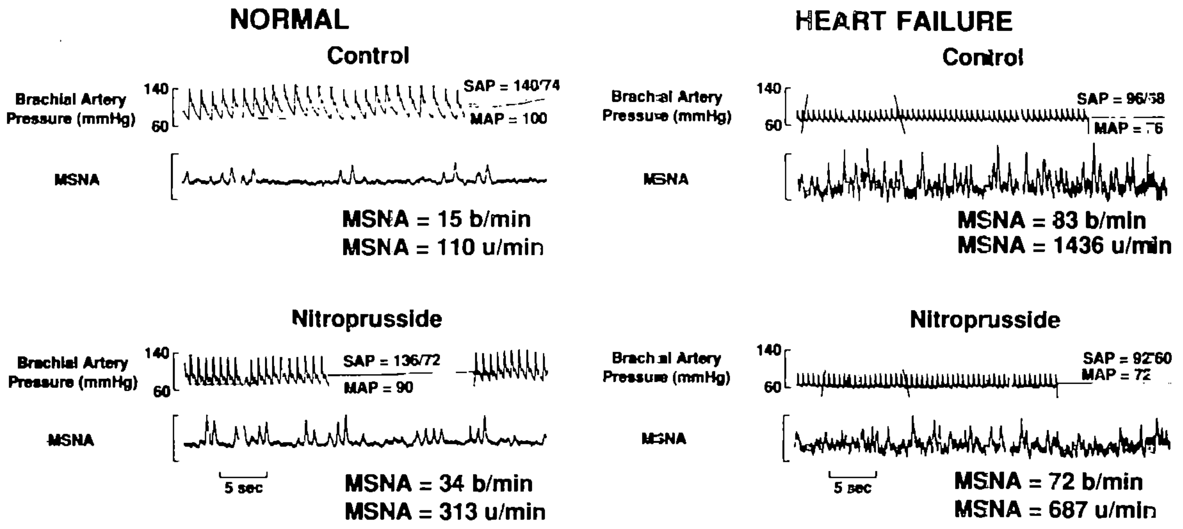

FIGURE 2. Comparative experimental recordings from a normal subject *(left panels)* and a patient with heart failure *(right panels)* during control conditions *(upper panels)* and during baroreceptor unloading with intravenous nitroprusside *(lower panels)*. Despite similar nitroprusside-induced decreases in arterial pressure and cardiac filling pressure, the normal subject demonstrated significant increases in muscle sympathetic nerve activity (MSNA), whereas the patient with heart failure was unable to achieve sympathoexcitation; in this patient, nitroprusside actually produced a decrease in sympathetic bursts frequency and total integrated sympathetic activity. b/min = bursts per minute; MAP = mean arterial pressure; SAP = systemic arterial pressure.

jects (+14.7 ± 2.1%/mm Hg, $p < 0.001$). Similarly, when expressed as change in total integrated nerve activity (%) divided by nitroprusside-induced change in right atrial pressure (mm Hg), the heart failure patients exhibited a significantly diminished sensitivity (+9.7 ± 4.5%/mm Hg) compared with normal subjects (+59.8 ± 20.5%/mm Hg, $p < 0.05$).

Figure 2 presents experimental recordings from a normal subject (left panels) and a heart failure patient (right panels) during control conditions (upper panels) and during baroreceptor unloading with intravenous nitroprusside (lower panels). Despite similar decreases in arterial and cardiac filling pressures, the normal subject demonstrated significant sympathoexcitation, whereas the heart failure patient failed to exhibit sympathoexcitation. In this heart failure patient, nitroprusside actually produced a decrease in sympathetic burst frequency and total integrated sympathetic activity.

DISCUSSION

The unique feature of the present investigations was the use of direct assessment of efferent sympathetic neural activity to muscle during acute perturbations of baroreflexes in patients with heart failure. These studies indicate that patients with moderate to severe heart failure clearly have impaired heart rate and sympathetic nerve excitatory responses to acute baroreceptor deactivation. In addition, the heart failure patients also appear to demonstrate a tendency toward impaired heart rate and sympathetic neural responses to baroreceptor activation.

Comparison with other studies in patients with heart failure: Prior studies in heart failure patients demonstrate impaired cardiopulmonary baroreflex-mediated vasoconstrictor responses to orthostatic stress produced by lower body negative pressure, tilt-table or administration of vasodilators.[12,15,16,26] Similarly, attenuated plasma norepinephrine responses to administration of vasodilators have also been observed.[14,27,28] Although not conclusive, preliminary studies suggest that the degree of impairment of these responses reflects the severity of underlying cardiac dysfunction[13,14,29,30] and may be related to prognosis in this condition.[27] Patients with cardiac dysfunction have also been noted to have abnormalities in arterial baroreflex control of heart rate.[10,11,27,31] Studies using ambulatory heart rate variability in patients with chronic heart failure have suggested impairment of cardiac vagal influences.[32] Preliminary studies from our laboratory suggest that this parasympathetic dysfunction is related to the magnitude of sympathoexcitation in heart failure.[33]

In all these prior studies of heart failure patients, the effector limbs of the cardiopulmonary and arterial baroreflexes have been *indirectly* assessed by examining vascular, heart rate or neurohormonal responses during acute baroreflex perturbations. Such indirect assessments make it difficult to define the mechanism(s) involved. For example, it is possible that abnormalities in baroreflex control of vascular resistance might reflect alterations in end-organ responsiveness (e.g., vascular stiffness) rather than impairment of baroreflex mechanisms. Similarly, plasma norepinephrine reflects not only the level of sympathetic neural activity, but also the variability of regional release and clearance of this catecholamine, variability of sampling sites, and the potential influence of concomitant pharmacologic agents on norepinephrine kinetics or autonomic mechanisms, or both. Any of these factors may be operative in patients with heart failure. Further, these prior studies have not controlled for the potential influence of concomitant drug administration on norepinephrine kinetics or baroreflex mechanisms in the heart failure state because these studies have often examined patients being maintained on chronic pharmacologic therapy (e.g., digitalis glycosides) known to alter baroreflex mechanisms.[15,21] Based on such indirect assessment of neuroeffector responses, these earlier studies suggested impairment of baroreflex mechanisms in heart failure. However, recent animals studies that directly examined efferent sympathetic neural responses during baroreflex perturbation have demonstrated impaired parasympathetic control of heart rate responses, but preserved baroreflex control of sympathetic nerve activity under conditions of baroreceptor activation in both low and high output models of heart failure.[17,18]

The present studies were therefore designed to avoid many of the limitations inherent in the prior clinical investigations. In the present study, *direct* measurements of efferent sympathetic nerve activity and heart rate responses were obtained during acute activation and deactivation of baroreceptors. These studies were performed in clinically stable patients with moderate to severe heart failure who were not receiving medications known to alter autonomic mechanisms. Patients were excluded from the study if they had any other disorders, other than heart failure, known to be associated with abnormalities of sympathetic control mechanisms. The results of the present study demonstrate impaired heart rate and sympathetic nerve responses to baroreceptor deactivation with nitroprusside, and are consistent with the impaired heart rate and norepinephrine responses to vasodilator infusion reported by Olivari et al.[27]

Potential mechanisms of impaired sympathoexcitatory responses in heart failure: Inherent limitations in performing neurocirculatory studies in intact human subjects make it difficult to precisely define the mechanisms of the impaired sympathoexcitatory responses observed in the present studies. However, important new insight can be gained from these first studies to directly examine efferent sympathetic nerve activity responses in heart failure patients. Muscle sympathetic nerve activity is regulated primarily by baroreflex, chemoreflex and somatic reflex mechanisms.[19,20,22-24] The present studies were performed in patients at rest in the absence of hypoxemia, hypercarbia or acidosis, suggesting that somatic and chemoreflex responses were not contributing significantly to the observed changes in sympathetic nerve activity. These studies therefore suggest that the attenuated heart rate and sympathetic neural responses of patients with heart failure during infusions of phenylephrine and nitroprusside result from an impairment of arterial or cardiopulmonary baroreflex mechanisms, or both. The present findings are consistent with prior demonstration of impaired vasoconstrictor and neuroendocrine responses to unloading of cardiopulmonary and arterial baroreceptors with techniques such as lower body negative pressure, tilt-table, or vasodilator infusion.[12,14,16,26,28] Such impairment could arise as a result of abnormalities in the structure of afferent baroreceptor sensory endings, abnormalities in the neurohormonal mileu of these sensory endings, or alterations in the compliance of the arterial and cardiac walls containing these mechanoreceptors. With respect to the heart rate responses, an additional factor might be a desensitization of the sinoatrial nodal tissue to endogenous stimulation as previously described in humans.[34]

We considered the possibility that the inability of patients with heart failure to increase sympathetic nerve activity in response to nitroprusside might simply be a reflection of an inability to further increase nerve activity above markedly elevated baseline level or a generalized central suppression of reflex responsiveness. However, these possibilities seem unlikely because recent studies in our laboratory have clearly demonstrated that heart failure patients with similar levels of sympathetic nerve activity at rest can significantly increase neural activity in response to the non-baroreflex-mediated sympathoexcitatory stimulus of the cold pressor test.[35]

Potential limitations of present studies: We recognize several potential limitations in the interpretation of these studies. First, all measurements were performed in supine subjects at rest in a temperature-controlled environment. The relations between hemodynamic and sympathetic nerve parameters may be different during states of circulatory stress such as exercise or upright posture. Second, measurements of sympathetic nerve activity were derived from only 1 site, the peroneal nerve. Differences are known to exist in the control of sympathetic nerve activity to various tissues and vascular beds.[23,24] However, at least in normal subjects at rest, spontaneously occuring fluctuations in muscle sympathetic nerve activity are remarkably similar in different sites on the arm and leg[25] and baroreflex-mediated changes in muscle sympathetic nerve activity are similar in the arm and leg when measured simultaneously.[36] Third, patients with heart failure as a group were older than normal subjects. Although experimental data suggest an attenuation of baroreflex function with age,[37,38] we believe it unlikely that the differences in ages between the normal subjects and heart failure patients alone can explain the results of these studies. As noted in prior studies from our laboratory,[3,4] resting levels of sympathetic nerve activity in "young" patients with heart failure are significantly greater than that observed in age-matched normal subjects. In the present study, 4 of the 11 patients with heart failure studied were ≤35 years of age. Furthermore, there appeared to be no relation between the age of a heart failure patient and the magnitude of impairment of baroreflex sympathoexcitatory responses. No correlation was observed in the heart failure patients between baroreflex sensitivity and age when expressed as either percent change in sympathetic nerve activity per mm Hg decrease in mean arterial pressure ($r = 0.47$, $p = 0.17$, $n = 10$) or right atrial pressure ($r = 0.48$, $p = 0.16$, $r = 10$) during infusion of nitroprusside.

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Effect of Captopril on Cardiac Parasympathetic Activity in Chronic Cardiac Failure Secondary to Coronary Artery Disease

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Thirty-two patients with chronic cardiac failure underwent 24-hour ambulatory electrocardiographic monitoring on 2 separate occasions: 20 patients before and during treatment with captopril, and 12 acting as controls. Heart rate variability was calculated by counting the number of times successive RR interval differences were >50 ms (this measurement being a reliable index of cardiac parasympathetic activity). During treatment with captopril, group mean total counts increased to 1,032 (range 48 to 7,437) from 482 (range 23 to 6,120) (p = 0.002). There was no change in mean hourly waking or sleeping heart rates. In the control group, no changes were seen: group mean total counts on the first occasion were 340 (range 120 to 3,255) and on the second occasion 400 (range 154 to 3,300) (p = not significant). These results show that treatment with angiotensin-converting enzyme inhibitors increases cardiac parasympathetic activity in patients with chronic cardiac failure. This may be relevant to the improved prognosis of this group of patients when treated with angiotensin-converting enzyme inhibitors.

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The beneficial effect of adding angiotensin-converting enzyme inhibitors to diuretics on symptoms[1] and prognosis[2] in patients with chronic cardiac failure is well-established. Although other vasodilators improve prognosis,[3] troublesome symptoms often occur[3] together with a reflex tachycardia despite a reduction in blood pressure.[4] Studies in hypertensive[5] and normal[6] subjects suggest that angiotensin-converting enzyme inhibitors may increase parasympathetic activity, possibly by inhibiting the formation of angiotensin II, which interacts extensively with autonomic nerves[7] and may have a peripheral vagolytic effect.[8]

Patients with chronic cardiac failure may have impaired parasympathetic function at an early stage of the disease,[9] and reduced heart rate variability as assessed by either power spectral analysis[10] or mean hourly heart rate standard deviation.[11] We previously described another way to measure heart rate variability, using 24-hour ambulatory heart rate monitoring.[12-14] Our aim in this study was to determine whether in patients with cardiac failure, the introduction of captopril altered heart rate variability and hence, cardiac parasympathetic activity.

METHODS

Patients: Thirty-two patients with chronic cardiac failure due to coronary artery disease were studied. All were in sinus rhythm. None had evidence of diabetes or renal failure, and there had been no sudden change in clinical state, or myocardial infarction in the previous 6 weeks. All patients remained symptomatic (New York Heart Association functional class III) despite a sodium restricted diet (120 mmol/day) and diuretic therapy. No patient was receiving digoxin. Patients were divided into 2 groups, 1 receiving captopril, and the second acting as a control group. In the captopril group there were 20 patients (15 men, mean age 63 ± 8 years, range 38 to 70; mean cardiothoracic ratio 52%, range 48 to 56). Mean radionuclide left ventricular ejection fraction was 19 ± 7% (range 8 to 32). Mean daily furosemide dose was 100 ± 14 mg (range 80 to 120). Twelve patients acted as controls (10 men, mean age 62 ± 8 years, range 46 to 71; mean cardiothoracic ratio 50%, range 48 to 52). Mean radionucleotide left ventricular ejection fraction was 19 ± 4% (range 15 to 28). Mean daily furosemide dose was 88 ± 12 mg (range 80 to 120).

Protocol: Twenty-four-hour ambulatory electrocardiographic monitoring was performed on 2 separate oc-

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casions. Patients were first monitored before admission to the hospital, and then again within 48 hours of discharge.

Each patient was admitted to the hospital for 24 hours. For those patients receiving captopril, the maintenance oral diuretic was omitted and each patient received a test dose of captopril (6.25 mg at 0900 hours). If this was well-tolerated, increasing doses of captopril were administered (12.5 mg at 1400 hours, and 25 mg at 2200 hours). No patient developed symptomatic hypotension during the introduction of captopril. The next day, the maintenance dose of furosemide was restarted in addition to captopril (25 mg 3 times daily). Patients were mobilized around the ward and discharged after the second dose of captopril at 1400 hours. Further 24-hour ambulatory monitoring was then performed. On both occasions, patients performed their normal daily activities. The times of going to bed and waking up were recorded by each patient.

The patients in the control group followed the same protocol as those in the captopril group, but they did not receive captopril, and on the following day had their diuretic dose increased by 40 mg/day.

Study methods: Twenty-four-hour ambulatory electrocardiographic monitoring was performed using a portable tape recording system (TRACKER, Reynolds Medical Limited, Hertford, England). Tapes were later replayed through a Pathfinder arrhythmia analyzer (Reynolds) at 120X the original recording speed, and heart rate variability was measured as previously described in detail.[12,13] Our method identifies and excludes ventricular ectopic beats, even in large numbers.[13] Successive beat-by-beat RR interval differences >50 ms are calculated as either positive (increasing) or negative (decreasing) "counts." Because we previously found similar values for increasing and decreasing counts,[12] the values given in this study are for positive counts only. Results are presented as total 24-hour counts, mean hourly waking and sleeping counts, and mean hourly waking and sleeping heart rates. We excluded records of <18 hours of duration, and those in which <40% of the tape was analyzable. Because tapes did not always run for exactly 24 hours, the totals were rounded up to the equivalent of 24 hours in all cases.

In a population of normal individuals, the approximate lower 95% tolerance limits for 24-hour counts are 2,000 at 25 years, 1,000 at 45 years, and 500 at 65 years.[14]

Statistical analysis: The data for counts were markedly skewed, and therefore logarithmic transformation was performed. Paired *t* tests were used to compare both counts and heart rates. Mean differences and 95% confidence intervals for them were calculated. Results are presented as geometric mean for counts and as arithmetic means for heart rates.

RESULTS

In the control group, mean total 24 hour counts were similar on both occasions (first: 340, range 120 to 3,255; second: 400, range 154 to 3,300; p = 0.275). Mean hourly waking and sleeping heart rates were also similar on the 2 occasions (Table I).

TABLE I Group Mean 24-Hour Counts and Heart Rates in 32 Patients with Chronic Cardiac Failure: Before (tape 1) and During (tape 2) Treatment with Captopril, and Receiving Diuretics Alone on Two Separate Occasions (tapes 1 and 2)

	Tape 1	Tape 2	p Value	Mean Difference	95% CI
Captopril Group (n = 20)					
Group mean total 24-hr counts	482	1,032	0.002	0.467	0.296–0.736
Mean hourly waking counts	14	24	0.018	0.561	0.351–0.899
Mean hourly sleeping counts	16	39	0.018	0.427	0.214–1.175
Mean hourly waking HR	85	83	0.112	1.85	−0.479–4.179
Mean hourly sleeping HR	76	73	0.075	2.45	−0.247–5.147
Control Group (n = 12)					
Group mean total 24-hr counts	340	400	0.275	0.847	0.618–1.164
Mean hourly waking counts	10	13	0.239	0.755	0.459–1.242
Mean hourly sleeping counts	19	21	0.529	0.92	0.693–1.222
Mean hourly waking HR	82	83	0.608	−0.833	−4.312–2.645
Mean hourly sleeping HR	77	75	0.660	1.583	−6.145–9.311

CI = confidence interval; HR = heart rate.

Group mean total 24-hour counts increased significantly in patients treated with captopril from 482 (range 23 to 6,120) to 1,032 (range 48 to 7,437) (p = 0.002). The total number of counts in 24 hours did not increase during captopril treatment in only 3 patients (Figure 1). Mean hourly waking (14 to 24; p = 0.018) and sleeping (16 to 39; p = 0.018) counts also increased significantly during treatment with captopril. By contrast there was no change in mean heart rate with treatment (waking: before 85 ± 15, and after 83 ± 14 beats/min; sleeping: before 76 ± 14, and after 73 ± 12 beats/min; Table I).

DISCUSSION

We demonstrated increased heart rate variability during treatment with captopril in patients with chronic cardiac failure. Our counts method for measuring heart rate variability is an accurate and reliable index of cardiac parasympathetic activity[12,14,15] and is reproducible in patients with cardiac and other diseases.[12-14] Therefore, our results imply that treatment with an angiotensin-converting enzyme inhibitor is associated with an increase in cardiac parasympathetic activity in these patients. Although we cannot completely exclude the possibility that the change was simply due to improvement in the clinical state, there are good reasons for believing

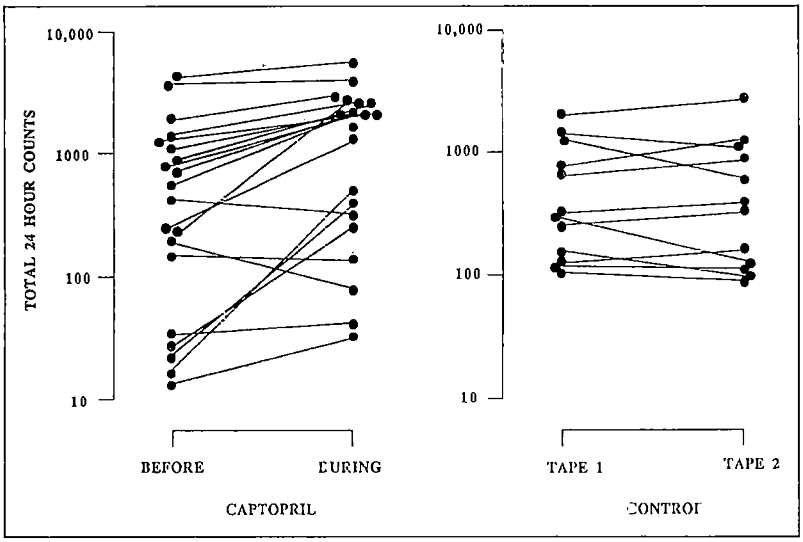

FIGURE 1. Individual total 24-hour counts in 20 patients with chronic cardiac failure before and during treatment with captopril, and in 12 with cardiac failure receiving diuretics alone.

this to be a genuine effect of captopril treatment. The results from our control group show that by using the same protocol, no significant alteration in counts occurred despite an increase in diuretic treatment and an improvement in clinical state.

Abnormalities of parasympathetic activity have been reported in patients with chronic cardiac failure after pharmacologic and physiologic interventions.[9] Decreased heart rate variability was also described in patients with cardiac failure,[10,11] supporting our own observations of decreased cardiac parasympathetic activity.[16]

Captopril, unlike other vasodilators administered to patients with cardiac failure, does not produce a reflex tachycardia.[17] In studies using an airtight neck chamber to stimulate the carotid sinus baroreceptors in patients with cardiac failure, 1 dose of captopril seemed to augment a reflex bradycardia through an increase in efferent vagal activity.[18] There are several different potential sites where the renin-angiotensin system interacts with the autonomic nervous system. Angiotensin II enhances noradrenaline release from both pre-[19] and postsynaptic[20] sympathetic nerve terminals in vitro, although this has not been demonstrated in humans,[21] and inhibits vagal discharge peripherally in dogs.[10] In normal human subjects, enhanced vagal activity after the administration of angiotensin-converting enzyme inhibitors may be a direct consequence of removal of the vagolytic action of angiotensin II.[8] Angiotensin II may also act centrally to inhibit efferent parasympathetic activity,[22] possibly in the area postrema.[23] However, it is not known whether captopril crosses the blood-brain barrier to inhibit the production of brain angiotensin II.[24]

The effect of captopril that we have shown on heart rate variability may partly explain its effect on ventricular arrhythmias in patients with cardiac failure.[25] Previously it was suggested that increases in plasma potassium concentration and decreases in circulating catecholamine concentration were responsible,[25] but we would speculate that increased parasympathetic activity is as important in preventing the development of ventricular arrhythmias.[26] Decreased heart rate variability has been linked to poor prognosis in patients after myocardial infarction.[27] We suggest that increased heart rate variability and, therefore, cardiac parasympathetic activity may be important factors in the improved prognosis of cardiac failure when it is treated with angiotensin-converting enzyme inhibitors.

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Late (Two-Year) Follow-Up After Percutaneous Balloon Mitral Valvotomy

Peter C. Block, MD, Igor F. Palacios, MD, Elizabeth H. Block,
E. Murat Tuzcu, MD, and Brian Griffin, MD

Percutaneous balloon mitral valvotomy (PBMV) compares well with surgical commissurotomy, showing comparable improvement in symptoms and catheterization-proven valve area early after the procedure. This study reports the New York Heart Association class, mitral valve area calculated by echocardiography, and the results of transseptal cardiac catheterization 2 years after PBMV. The data are compared with the status immediately before and after PBMV. Forty-one patients returned to enter the study (mean follow-up time 24 ± 3 months). All patients were evaluated clinically by the same investigator who had seen them at the time of PBMV. Transseptal cardiac catheterization and echocardiographic analysis (2-dimensional and Doppler echocardiography) were performed on the same day. At follow-up, 17 patients were class I, 20 were class II, and 4 were class III. Although the mitral valve area calculated by cardiac catheterization increased significantly from immediately before to immediately after PBMV there was a decrease in the calculated mitral valve area at 2-year follow-up. Echocardiographic analysis did not show as large an increase in mitral area, immediately after PBMV, and no significant decrease in mitral valve area at 2 years (before PBMV planimetry 1.1 ± 0.1 cm^2; immediately after 1.8 ± 0.1 [$p < 0.05$]; follow-up 1.6 ± 0.1 [p = not significant compared with immediately after PBMV]). Doppler halftime measurements were similar. PBMV is effective therapy with good midterm results for selected patients with mitral stenosis.

(Am J Cardiol 1992;69:537–541)

Percutaneous balloon mitral valvotomy (PBMV) produces prompt improvement of symptoms for many patients with mitral stenosis.[1–7] Studies comparing PBMV with closed surgical commissurotomy have shown comparable improvement in symptoms and catheterization-proven valve area early after PBMV.[8] However, longer term results are needed to evaluate the usefulness of PBMV. In this study we report the New York Heart Association class, mitral valve area calculated by echocardiography, and the results of transseptal cardiac catheterization 2 years after PBMV in a cohort of sequential patients. The data are compared with New York Heart Association class, and echocardiographic and catheterization data in the same patients immediately before and after PBMV.

METHODS

The aim of this study was to collect data on 40 sequential patients in the same institution, as close to 2 years after PBMV as possible. In September 1989, patients who underwent PBMV beginning on September 1, 1987 were contacted sequentially and asked to return to Massachusetts General Hospital for follow-up clinical evaluation, transseptal cardiac catheterization and echocardiography. From September 1, 1987 through July 27, 1988, 82 patients underwent PBMV. Forty-one patients returned to enter the study at a mean follow-up time of 24 ± 3 months.

Clinical evaluation: All patients were seen by the same investigator who had evaluated them at the time of PBMV. Clinical evaluation was based on New York Heart Association classification for congestive heart failure.

Cardiac catheterization: All patients underwent outpatient right, transseptal and left heart catheterization. Unless contraindicated, left ventricular cineangiography was performed either retrograde using a pigtail catheter, or anterograde using a Berman catheter (Arrow International, Reading, PA). Oximetry was performed during right heart catheterization to evaluate left-to-right shunting. Mitral valve area was determined using the Gorlin equation. Values were compared with catheterization data obtained 2 years before. If a left-to-right shunt was found (defined as a step-up in oxygen saturation between superior vena cava and pulmonary artery samples of ≥ 7 volumes percent), the Fick method for calculation of cardiac output was used. Ventriculograms were evaluated for left ventricular ejection fraction and the amount of mitral regurgitation. These were com-

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pared with the left ventriculograms obtained immediately after PBMV 2 years before.

Echocardiographic analysis: Patients were studied with 2-dimensional and Doppler echocardiography <24 hours before PBMV, <48 hours after and at the time of admission for 2-year follow-up. All 41 patients had echocardiographic and Doppler data obtained before PBMV and during 2-year follow-up. Thirty-two patients had echocardiograms obtained immediately after PBMV. In each study, standard echocardiographic images were obtained in the parasternal long- and short-axis, and apical 2- and 4-chamber views. All echocardiographic measurements were analyzed without knowledge of catheterization data. Mitral valve area was measured by direct planimetry of the valve orifice with a commercially available digitizing system from the smallest orifice of the valve, obtained in early diastole in the parasternal short-axis view. Mitral valve area was also calculated with the use of the pressure halftime method from the continuous-wave Doppler profile. Both methods of obtaining mitral valve area were used where possible. Planimetry was not possible for technical reasons in 2 of 41 patients examined before PBMV, in 4 of 30 immediately after and in 3 of 41 during follow-up. Adequate pressure halftime measurements were obtained in 31 of 41 patients before PBMV, in 20 immediately after and in 38 during follow-up.

The morphologic features of the stenotic mitral valve and subvalvular apparatus were evaluated with the use of a semiquantitative approach that we have previously described.[9,10] Scores ranging from 0 to 4 were assigned to represent each of 4 morphologic characteristics: leaflet rigidity, thickening, calcification and subvalvular thickening. Higher scores represent more severe morphologic abnormalities. The scores of the 4 individual features were added in each patient to obtain a total echocardiographic score.

Study patients: Forty-one patients (32 women and 9 men, mean age 52 ± 2 years, range 28 to 74) returned and were entered into the study. Before PBMV, no patient was New York Heart Association class I, 13 were class II, and 28 were class III (Figure 1). Sinus rhythm was present in 22 patients (54%), 19 (46%) were in atrial fibrillation, and 8 had previous surgical commissurotomy. At the time of PBMV, 30 patients (73%) had no calcium seen fluoroscopically, 8 (20%) had 1+ calcium within the mitral valve, and 3 (7%) had 2+ calcium. Patients with echocardiographic scores ≤8 have better immediate and short-term outcomes after PBMV than do those with higher scores.[9,10] Therefore, we analyzed this study cohort similarly. The echocardiographic "score" was ≤8 in 29 patients (70%), and >8 in 12 patients (30%). Before PBMV, 32 patients had no mitral regurgitation, 7 had 1+ mitral regurgitation, and 2 had 2+. Immediately after PBMV, 17 patients had no mitral regurgitation, 14 had 1+, 7 had 2+, and 3 had 3+.

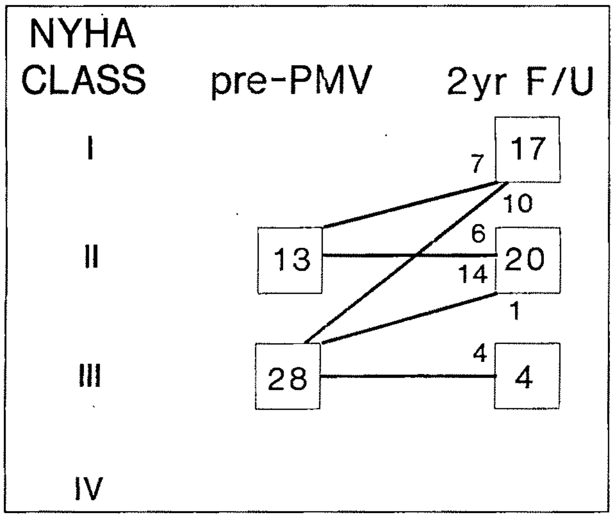

FIGURE 1. Changes in New York Heart Association (NYHA) classification before percutaneous mitral valvotomy (PMV) to 2 years after. At follow-up (F/U), 90% of patients are in NYHA class I or II.

Reasons for refusal to enter the study; demographics of patients who refused: Forty-one of the 82 sequential patients (33 women and 8 men, mean age 65 years, range 25 to 82) did not return for 2-year follow-up. Before PBMV, 5 patients were New York Heart Association class IV, 27 were class III, 8 were class II, and 1 was class I. Twenty-two patients had an echocardiographic score ≤8 before PBMV, and 19 patients scored >8. The reasons for refusing to return were as follows: refused repeat catheterization (14 patients), contraindication to catheterization (9), lost to follow-up outside of the U.S. (2), catheterization performed elsewhere (1), unable to be admitted on planned day and returned home (1), death between PBMV and follow-up date (6), and mitral valve replacement (8). Patients at the time of follow-up who did not return were contacted by phone on their follow-up date for a New York Heart Association class evaluation. Thirteen were New York Heart Association class I, 4 were class II, and 8 were class III.

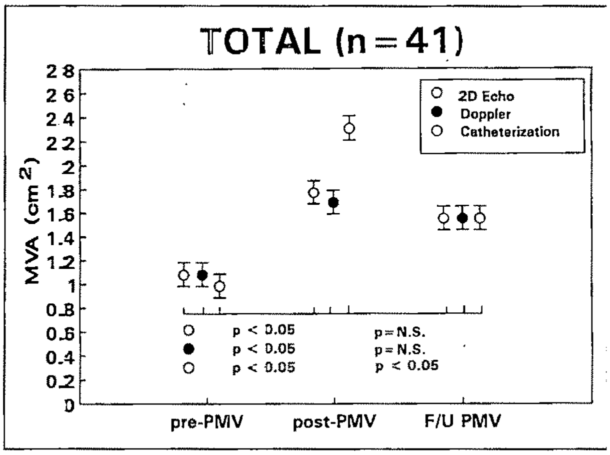

FIGURE 2. Mitral valve area (MVA) before (pre-) and immediately after (post-) percutaneous mitral valvotomy (PMV), and at 2-year follow-up (F/U) determined by cardiac catheterization, 2-dimensional echocardiography (2D Echo) and Doppler halftime. The 3 techniques result in similar values, except post-PMV. All values are significantly different pre- compared with post-PMV (p <0.05). There is no significant difference (p = not significant [N.S.]) in echocardiographically determined MVA post-PMV and at 2-year F/U, but MVA by cardiac catheterization is significantly lower at F/U (p <0.05).

RESULTS

Clinical evaluation: Changes in New York Heart Association classification before PBMV to 2 years later are shown in Figure 1. At follow-up, 17 patients were class I, 20 were class II, and 4 were class III.

Cardiac catheterization analysis: Mitral valve areas calculated by the Gorlin equation at cardiac catheterization, before, immediately after and at 2-year follow-up are shown in Figure 2. Although the mitral valve area increased significantly from immediately before to immediately after PBMV ($p < 0.05$) there was a decrease in the calculated mitral valve area at 2-year follow-up to 1.5 ± 0.1 cm^2 ($p < 0.05$ compared with immediately after PBMV). For patients with echocardiographic scores ≤ 8 ($n = 28$), the results are shown in Figure 3A. Mitral valve area immediately after PBMV was slightly greater than that in patients with echocardiographic scores >8 ($n = 13$) (Figure 3B). Mitral valve area during 2-year follow-up was also larger in patients with echocardiographic scores <8 (Figure 3, A and B). If one defines restenosis as a decrease >50% of the gain in mitral valve area achieved at the time of PBMV, by cardiac catheterization criteria 19 patients had no restenosis, 21 had restenosis, and 1 did not have adequate data for mitral valve calculation at follow-up.

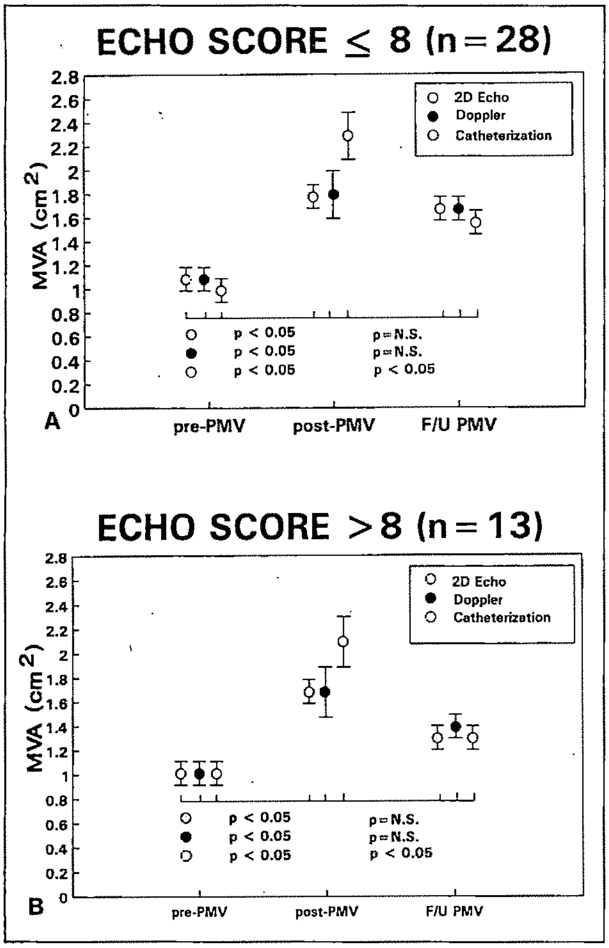

FIGURE 3. ***A,*** **mitral valve area (MVA) determined by 2-dimensional echocardiography (2D Echo), Doppler halftime and cardiac catheterization before (pre-) and immediately after (post-) percutaneous mitral valvotomy (PMV), and at 2-year follow-up (F/U) in patients with echocardiographic scores ≤8. Cardiac catheterization determination of MVA post-PMV is higher than echocardiographically derived MVA. There is little change from post-PMV to 2-year F/U in mitral valve area determined by echocardiography.** ***B,*** **MVA pre- and post-PMV, and at 2-year F/U determined by 2D Echo, Doppler halftime and cardiac catheterization in patients with echocardiographic scores >8. Findings are similar to those in Figures 2 and 3A. However, there is smaller MVA determined by all 3 techniques at 2-year F/U. Although not significantly different by echocardiographic comparisons, there appears to be a tendency toward restenosis in this subgroup of patients.**

There was no change in the calculated ejection fraction immediately after PBMV and at 2-year follow-up (mean left ventricular ejection fraction 70 ± 11 immediately after PBMV vs 62 ± 10 at 2-year follow-up; p = not significant). The amounts of mitral regurgitation seen by left ventricular cineangiography before, and immediately and 2 years after PBMV are shown in Figure 4. There was little change in the degree of mitral regurgitation from immediately after PBMV to 2 years later, although 4 more patients had 3+ mitral regurgitation at follow-up.

Echocardiographic analysis: For the entire group ($n = 41$) planimetry of the mean mitral valve area was 1.1 ± 0.1 cm^2 before PBMV, increasing to 1.8 ± 0.1 immediately after ($p < 0.05$). At follow-up, the valve area was 1.6 ± 0.1 cm^2 (p = not significant compared with immediately after PBMV; Figure 2). Doppler halftime measurements were similar (1.1 ± 0.1 cm^2 before PBMV, 1.7 ± 0.1 immediately after [$p < 0.05$]; 1.6 ± 0.1 at 2-year follow-up [p = not significant compared with immediately after PBMV]). The results of echocardiography for patients with echocardiographic scores ≤ and >8 are shown in Figure 3 (A and B). In both groups there was a significant increase in mitral valve area immediately after PBMV. The increase persisted at 2-year follow-up. In patients with echocardiographic scores ≤8 there was no trend toward restenosis. In patients with echocardiographic scores >8, the difference between mitral valve areas calculated by echocardio-

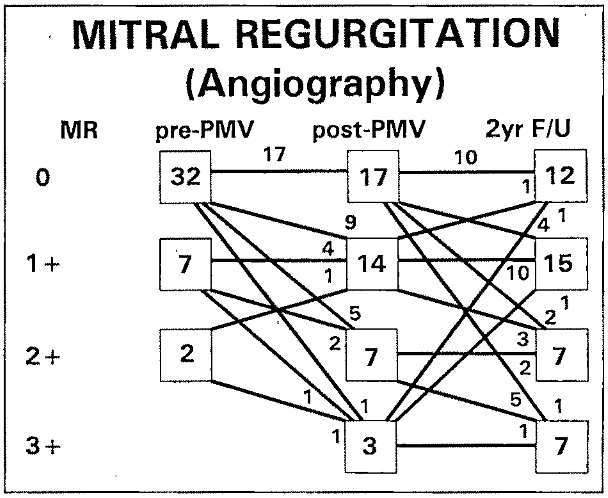

FIGURE 4. Mitral regurgitation (MR) evaluated by left ventricular cineangiography before (pre-) and immediately after (post-) percutaneous mitral valvotomy (PMV), and at 2-year follow-up (F/U). MR is increased by 1 grade in 27% of patients and by 2 grades in 20% after PMV. At 2-year follow-up, 4 more patients developed 3+ MR. Three patients (7%) had improvement in MR.

graphic techniques immediately after PBMV and during follow-up did not reach statistical significance, but there was evidence of a trend toward restenosis (defined as a decrease of 50% of the initial gain of mitral valve area 2 years after PBMV).

Because there was a range around the mean mitral valve areas calculated by echocardiography, an analysis of each patient was performed by both planimetry and Doppler halftime techniques to evaluate restenosis. By planimetry, 20 patients did not have restenosis, 7 had restenosis (4 with echocardiographic scores ≤ 8), and 14 had data that were not adequate for evaluation of mitral valve area either immediately after PBMV or at follow-up. By pressure halftime techniques, 21 patients did not have restenosis, 8 had restenosis (3 with echocardiographic scores ≤ 8), and 12 had data that was incomplete.

DISCUSSION

Our data show that PBMV provides ongoing improvement in clinical status 2 years after the procedure (41% of our patients are in New York Heart Association class I, and 49% are in class II). More than half (51%) of the patients remained 1 New York Heart Association class improved at 2-year follow-up, and 24% were improved 2 classes. It is no surprise that patients improved 2 years after PBMV, because PBMV results in splitting of fused commissures similar to that of surgical commissurotomy.[3,11,12] Long-term follow-up studies of surgical patients are based on clinical follow-up almost exclusively and show excellent improvement in symptoms after commissurotomy.[13,14] Of our patients who were not improved clinically, 50% had echocardiographic scores >8 (valves more thickened, calcified, rigid and with subvalvular disease). Grouping patients by echocardiographic score was used as a convenience for outcome analysis and should not imply that a score >8 predicts a poor outcome. Mitral valve area after PBMV is continuously, linearly dependent on echocardiographic score. Long-term outcome of PBMV in patients even with high echocardiographic scores can be unpredictable.

There is bias inherent in this kind of clinical analysis in that not all sequential patients returned for repeat evaluation and cardiac catheterization. The demographics of the group who did not return show that they were older and had more high echocardiographic scores than did the group that returned. Ninety percent of the patients who returned for follow-up were New York Heart Association class I or II. In contrast, only 63% (17 of 27) of the patients who did not return were in New York Heart Association class I or II. Age and the amount of mitral valve pathology are associated with a worse outcome,[9,10] and a less favorable outcome in this group would be expected.

Calculating the "true" mitral valve area immediately after PBMV is imprecise. Transseptal passage of 2 dilating balloons produces an atrial septal defect and left-to-right shunting, which increases right-sided cardiac output even though oxygen saturation measurements may not detect the shunt.[15] The atrial septal defect also decompresses the left atrium, lowering left atrial pressure. These 2 factors result in a calculation of mitral valve area that may be falsely high. If the atrial septal defect is occluded by a small balloon catheter, and repeat measurements are obtained immediately after PBMV, the mitral valve areas calculated by the Gorlin formula are similar to those calculated by pressure halftime or planimetry from the echocardiogram.[16] Using the Fick method to determine cardiac output may also be inaccurate due to rapidly changing hemodynamics immediately after PBMV, patient anxiety, and difficulty in obtaining simultaneous oxygen consumption and pressure measurements. At 2-year follow-up, most atrial septal defects have closed.[15] The mitral valve area calculated from cardiac catheterization data at that time is more likely a "true" mitral valve area.

Echocardiographic techniques are a more direct form of mitral valve area calculation and do not rely on cardiac output measurements. Both echocardiographic methods of assessing the mitral valve area are in good agreement with the area calculated by catheterization data before and 2 years after PBMV. However, immediately after PBMV there is poor agreement between the echocardiographic and cardiac catheterization methods. After PBMV, the mitral valve area measured during cardiac catheterization was generally larger than that measured using either of the echocardiographic techniques. There are also difficulties in assessing mitral valve area using echocardiographic methods immediately after mitral valvotomy. Planimetry should be the ideal method to determine the mitral valve area, in that it measures the mitral orifice at its anatomically narrowest point. However, it may be impossible to obtain adequate cross-sectional images of the mitral orifice, as was the case in a number of the patients in the present study. After PBMV planimetry may be technically more difficult owing to stretching and disruption of the valve. The pressure halftime method assumes that the Doppler pressure halftime has a simple linear inverse relation to the mitral valve area. However, other factors, such as compliance of the left atrium and ventricle, the peak pressure gradient across the mitral valve orifice, and the presence of concomitant aortic regurgitation, influence the pressure halftime independent of the mitral orifice area.[9]

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MISCELLANEOUS

Reproducibility of Quantitative Backscatter Echocardiographic Imaging in Normal Subjects

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Hewlett E. Melton, Jr., PhD, and Byron F. Vandenberg, MD

Cyclic backscatter variation is useful in differentiating normal from ischemic and myopathic myocardium; however, there are few data on the reproducibility of clinical cyclic variation measurements. Therefore, a study using 2-dimensional and M-mode backscatter imaging was performed in 20 normal male subjects by 2 observers at an initial session and by 1 of the observers after 1 week. Cyclic variation on M-mode was calculated as the difference between the end-diastolic backscatter and the backscatter at the nadir. Two-dimensional determinations of backscatter were made using a single frame at end-diastole and one at end-systole. The cyclic change was the difference between backscatter measured in the end-diastolic and end-systolic frames. There were no statistically significant differences in analysis of variance among the grouped repeated measurements in either the interventricular septum or the posterior left ventricular wall. At the initial session, cyclic backscatter variation in the posterior wall using M-mode techniques was 5.9 ± 1.8 dB (SD). The cyclic change in backscatter in the septal wall, using the 2-dimensional technique, was 4.3 ± 2.4 dB. In the posterior wall, the cyclic change in backscatter was 5.7 ± 1.7 dB. Pairwise observer correlations between repeated measurements ranged from −0.48 to 0.45. Thus, although there were no significant differences in group means on repeat measurements, repeated measurements in individual subjects were not reliably reproduced because of limited independent sampling of backscatter measurements at only 2 points in the heart cycle. Increased independent sampling and measurement from a backscatter waveform throughout the cardiac cycle may improve reproducibility of measurements.

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The measurement of ultrasound backscatter has been studied for noninvasive myocardial tissue characterization.[1-9] Backscatter varies with cardiac contraction, with minimal backscatter values occurring at end-systole.[4-6] Recent studies using measurements of cyclic backscatter variation have used an imaging system capable of displaying and measuring relative integrated backscatter throughout the heart cycle.[10] These studies have found that blunting of cyclic backscatter variation occurs in a spectrum of overlapping (i.e., acute ischemia, acute and chronic myocardial infarction) and dissimilar (i.e., left ventricular hypertrophy and cardiac allograft rejection) cardiac disorders.[11-16]

For the measurement of cyclic variation of relative integrated backscatter to have maximal clinical use, the reproducibility of the measurements is important. Studies concerning the reproducibility of backscatter data acquisition and measurement in normal subjects are limited.[14,17] Therefore, the purpose of the present study was to evaluate the inter- and intraobserver variability as well as longitudinal reproducibility for the entire process of data acquisition and determination of cyclic backscatter variation in normal subjects.

METHODS

Subjects: Twenty normal male volunteer subjects were studied. All subjects had a normal cardiac history and physical examination. Subjects were taking no medications at the time of study. Orthostatic (supine and sitting) blood pressure and heart rate were obtained at both imaging sessions. Subjects of approximately average height and weight were chosen to optimize the chances of obtaining good quality echocardiographic images. The study was approved by The University of Iowa Institutional Review Board and informed consent was obtained from all subjects.

Standard M-mode measurements: M-mode echocardiographic recordings for chamber dimensions were obtained with a 2-dimensional echo-guided cursor using a standard echocardiographic system employing a 2.5 MHz transducer. Chamber dimensions were obtained from either a parasternal long- or short-axis view, using criteria recommended by the American Society of Echocardiography.[18]

Backscatter imaging system: The two-dimensional echocardiographic backscatter imaging system used was modified from a commercial imaging system. A 2.5 MHz center frequency transducer with a 40% fractional band width was used (i.e., the band width of the frequency spectrum centered at 2.5 MHz is 1 MHz and is 40% of the center frequency). In addition to the display

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of conventional 2-dimensional images, the system generates gray level and color-coded real-time relative backscatter images and permits quantitative analysis of the frozen M-mode backscatter recording or, in the case of 2-dimensional backscatter, quantitative analysis within a selected region of interest of a frozen frame.

With this backscatter imaging system, relative integrated backscatter refers to the ratio of the ultrasound energy reflected from a myocardial region of interest ($E_{myocardium}$) to the value of an internal system reference standard ($E_{reference}$) and is defined as: Relative backscatter = 10 log($E_{myocardium}/E_{reference}$). This calculation differs from previous work[19,20] in which integrated backscatter was defined as the ratio of the energy from a tissue region of interest to the energy from a perfect (steel) reflector. Displayed gray levels in the present system bear a direct relation to relative integrated backscatter. The displayed dynamic range is 31.5 dB. The individual measurements of backscatter vary with the time-gain compensation setting; however, the relative magnitude of cyclic backscatter variation does not vary.

Digitized image (backscatter) data are stored within the imaging system and these data can be quantitatively evaluated by trackball-controlled, interactive programs also integral to the imaging system. Backscatter (in decibels) is measured from operator-defined regions of interest on the digitized image of the M-mode recording or of the 2-dimensional frame. Analysis of relative integrated backscatter is obtained from square (M-mode) and arbitrarily shaped (2-dimensional) regions on the respective freeze-frame images. The system displays electrocardiographic-triggered 2-dimensional images at any 2 operator-selected points in the heart cycle (in this study, end-diastolic and end-systolic frames) in a split-screen format (Figure 1). These 2-dimensional frame pairs were frozen, then used for the 2-dimensional backscatter measurements.

M-mode and two-dimensional backscatter data acquisition and analysis: Overall transmit power and time-gain compensation controls were adjusted to achieve a subjectively uniform brightness throughout the left ventricular myocardium. A time-gain compensation profile was established in the following manner: the gain controls affecting data from the interventricular septum were identified. Gain controls proximal to those used for the interventricular septum were then suppressed to minimize or eliminate near-field artifacts. All gain controls affecting the septum were adjusted the same to produce uniform brightness of the septum at a gain level that permitted the display of myocardial speckle but without "blooming" (saturation) of the endocardial/epicardial specular reflectors. Gain controls for the posterior left ventricular wall were then identified and adjusted to a level where the brightness of the posterior wall appeared subjectively similar to that of the septum. Gain controls for portions of the image distal to the posterior wall were suppressed to minimize or eliminate far-field artifacts. The overall transmit power was then adjusted to eliminate extraneous echoes from the ventricular cavity, the left atrium and the ascending aorta. The overall transmit power and time-gain compensation controls remained constant throughout a given image sequence for a particular subject.

Two-dimensional and M-mode backscatter imaging were performed only from the parasternal long-axis views with the subject in the left lateral decubitus position. Recent work from our laboratory has demonstrated cyclic variation of integrated backscatter to be view-dependent, differing between parasternal and apical images.[21]

During M-mode backscatter imaging, the M-mode recording was frozen (sweep speed = 50 mm/s) so that ≥2 cardiac cycles were included. Images were obtained in the parasternal long-axis view at the chordal level only. A square region of interest was adjusted to fit within the myocardium, excluding the specular reflectors, throughout the cardiac cycle. Relative backscatter was measured at end-diastole (defined as the backscatter at the onset of the QRS complex) and at end-systole (defined as the lowest value of backscatter following the QRS complex). Cyclic variation (in decibels) was the difference between the 2 values (Figure 2).

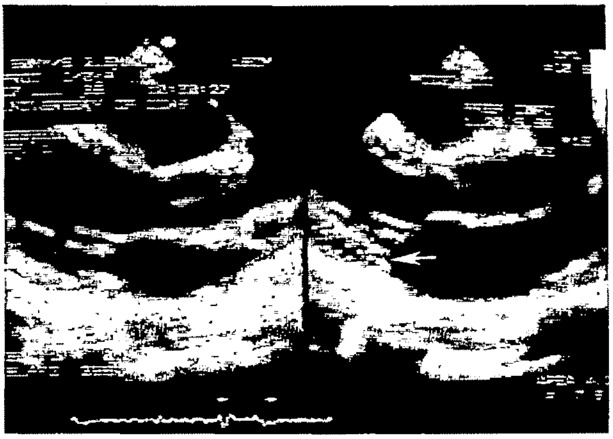

FIGURE 1. Quantitative backscatter 2-dimensional image of left ventricle (parasternal long-axis view) in end-diastole *(left)* and end-systole *(right)* obtained from parasternal long-axis view. Region of interest *(arrow)* for measurement of relative backscatter is placed in posterior wall of left ventricle at end-systole.

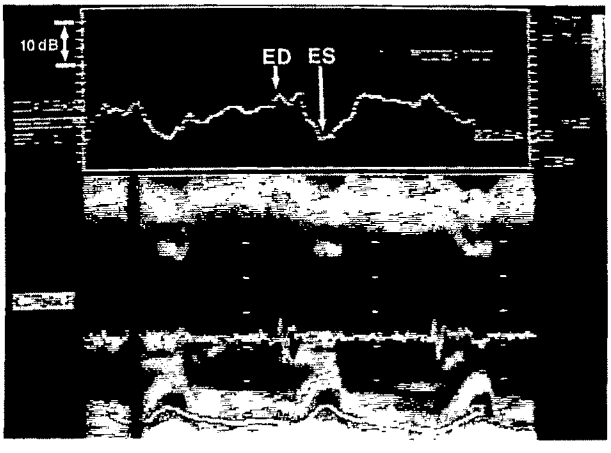

FIGURE 2. Determination of cyclic backscatter change from backscatter M-mode echocardiogram at the chordal level in the parasternal long-axis view. The analysis cell was moved by trackball through the posterior wall, avoiding specular reflectors. Backscatter decreased from end-diastole (ED) to end-systole (ES).

With the 2-dimensional imaging system, frames that corresponded to end-diastole (frame closest to the maximum slope of the onset of the QRS complex) and mechanical end-systole (frame corresponding most closely to initial closure of the aortic valve) were frozen. Arbitrarily shaped regions of interest were drawn into the myocardium of the basal septum and the basal posterior wall. To avoid variability in location or size of the region of interest, we placed the largest region of interest possible (≥0.5 cm^2), avoiding specular endocardial/epicardial reflectors in the myocardial regions. The cyclic change in backscatter was calculated as the relative backscatter within the end-diastolic region minus the relative backscatter within the end-systolic region. Thus, the difference in end-diastolic and end-systolic backscatter obtained with the 2-dimensional system is referred to as the cyclic change (rather than the cyclic variation) in backscatter, since backscatter nadir was not identified as it was in the M-mode approach.

Session I: inter- and intraobserver reproducibility: Cyclic backscatter variation is related to the contractile state of the myocardium.[4-6,22] Therefore, subjects were placed in the supine position for 10 to 15 minutes before imaging to allow attainment of a stable baseline hemodynamic state. Observer 1 (BFV) optimized patient position and machine settings as previously described. Two-dimensional integrated backscatter images (≥2 beats) were then obtained for backscatter analysis, followed by acquisition of ≥2 M-mode backscatter recordings (≥2 beats each). The subject was then returned to the supine position. The transmit power, time-gain compensation controls, depth controls, and the time delay switch for establishing end-systole (2-dimensional technique) were then set to their minimal values and the machine screen cleared. Observer 2 (JES) then completed the same sequence of data acquisition without knowledge of prior instrument adjustments or data. Once again, the patient was returned to the supine position and machine settings were returned to their minimal values at the completion of data acquisition. Observer 1 then completed a second study. The observers were unaware of each other's data acquisition. Therefore, the protocol allowed the assessment of inter- and intraobserver reproducibility.

Session II: longitudinal reproducibility: Repeat measurements were obtained 1 week later in all subjects. Subjects were screened for intercurrent illnesses by history. As in session I, the patients rested in the supine position for 10 to 15 minutes before imaging. Observer 1 obtained 2-dimensional and M-mode images for analysis in a manner identical to that outlined above for session I. Results of the backscatter measurements from session I were not reviewed in the intervening week, or during imaging in session II in order to minimize observer bias. Thus, longitudinal reproducibility could be assessed.

Statistical analysis: All data were reviewed independently by a third observer (DJS) who served as the final arbiter for the inclusion or exclusion of data. Criteria for exclusion included: improperly placed regions of interest that included specular reflectors, poorly visualized regions of interest and baseline artifacts on M-mode tracings. All data are expressed as mean ± standard deviation. The significance of differences across repeated measurements of cyclic backscatter variation for both 2-dimensional and M-mode measurements was examined using a repeated-measures analysis of variance.[23] Pearson product moment and Spearman rank order correlation coefficients were estimated for each of the following pairs of observations: observer 1 versus observer 2 at initial measurement session I (interobserver variability); observer 1 at initial measurement session I versus observer 1 at repeat measurement session I (intraobserver variability), and observer 1 at initial measurement session I versus observer 1 at session II (longitudinal reproducibility).[24] Observer variability was also estimated by calculating the mean absolute differences between observations. The significance of differences between groups was examined using 2-tailed *t* tests. For all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Subjects: Twenty consecutive men (age 29 ± 4 years) were studied. Physiologic measurements were obtained at session I: mean arterial pressure (supine) 86 ± 9 mm Hg, heart rate (supine) 53 ± 10 beats/min, height 178 ± 7 cm, weight 79 ± 10 kg, body surface area 1.97 ± 0.14 kg/m^2. At session II measurements were: mean arterial pressure (supine) 83 ± 7 mm Hg, heart rate (supine) 58 ± 7 beats/min, weight 79 ± 9 kg. There were no statistically significant differences between sessions in these measurements.

Measurements of cardiac chamber dimensions and wall thickness were normal in the study subjects. Average left ventricular end-diastolic dimension was 5.2 ± 0.6 cm, left ventricular end-systolic dimension was 3.4 ± 0.5 cm, percent fractional shortening was 35 ± 7%, interventricular septal thickness was 0.8 ± 0.2 cm, left ventricular posterior wall thickness was 0.7 ± 0.1 cm, left atrial dimension was 3.7 ± 0.5 cm, and aortic root dimension was 2.8 ± 0.3 cm. Two-dimensional echocardiograms were normal in all subjects.

Intraobserver and interobserver variability and longitudinal reproducibility: The data for both 2-dimensional and M-mode measurements are described in Table I.

Two-dimensional images: For the interventricular septum, there was no significant difference among the means of the 4 repeated measurements. Cyclic change in backscatter for the interventricular septum ranged from 0.0 to 10.0 dB. Mean absolute variabilities were 2.1 ± 1.3 dB (interobserver), 2.1 ± 1.9 dB (intraobserver) and 1.9 ± 1.3 dB (longitudinal).

For the posterior wall, there was no significant difference among the means of the 4 repeated measurements. Cyclic change in backscatter for the posterior wall ranged from 1.9 to 10.3 dB. Mean absolute variabilities were 2.4 ± 1.8 dB (interobserver), 1.5 ± 1.2 dB (intraobserver) and 1.4 ± 1.3 dB (longitudinal).

TABLE I Variability and Reproducibility of Group Data

	Session I			Session II
	OBS-1	OBS-2	OBS-1*	OBS-1†
	Two-Dimensional: Cyclic Change in Backscatter			
Septum	4.3 ± 2.4 n = 14 (0.8–8.8)	3.6 ± 2.3 n = 10 (0.5–7.5)	4.4 ± 2.4 n = 12 (1.0–10.0)	3.2 ± 1.7 n = 16 (0.0–6.0)
Posterior wall	5.7 ± 1.7 n = 19 (2.5–9.5)	4.4 ± 2.2 n = 16 (1.9–10.3)	5.7 ± 2.1 n = 19 (3.2–10.0)	5.1 ± 1.2 n = 19 (3.2–6.9)
	M-Mode: Cyclic Variation in Backscatter			
Posterior wall	5.9 ± 1.8 n = 18 (2.7–9.2)	5.6 ± 2.7 n = 13 (2.1–10.5)	5.3 ± 2.1 n = 13 (2.8–8.6)	5.5 ± 1.1 n = 13 (3.3–7.0)

*observer 1—repeat measurements session I.
†observer 1—repeat measurements session II (1 week later).
Data expressed as mean ± SD (range).
OBS-1 = observer 1; OBS-2 = observer 2.

M-mode images: M-mode cyclic backscatter variation from the interventricular septum was measurable in <5 subjects per imaging sequence and, therefore, statistical analysis of these data was not performed. For the posterior wall, there was no significant difference among the means of the 4 repeated measurements. Cyclic backscatter variation for the posterior wall ranged from 2.1 to 10.5 dB. Mean absolute variabilities were 2.8 ± 1.7 dB (interobserver), 1.6 ± 1.4 dB (intraobserver) and 1.9 ± 1.3 dB (longitudinal).

The range of r values for the pairwise observer correlations for longitudinal reproducibility, as well as inter- and intraobserver variability by 2-dimensional imaging, ranged from 0.03 to 0.45; by M-mode imaging, r values ranged from −0.48 to 0.39.

DISCUSSION

Previous clinical studies indicate that the cardiac cycle-dependent variation in relative integrated backscatter is sensitive for the detection of a variety of abnormal cardiac conditions: acutely ischemic[11] and infarcted myocardium,[11–13] idiopathic dilated cardiomyopathy[14] and left ventricular hypertrophy.[15] Most studies of patients with ischemic heart disease have compared backscatter cyclic variation in acutely ischemic or infarcted myocardium with the cyclic variation in remote, normal regions in the same patient. Backscatter cyclic variation in regions of acute ischemia or infarction ranges from 0.8 to 1.8 dB while cyclic variation in normal regions of myocardium ranges from 3.2 to 4.8 dB.[11–13] Studies in patients with idiopathic dilated cardiomyopathy and left ventricular hypertrophy have been cross-sectional in design, comparing backscatter cyclic variation measured in patients to values obtained in normal control subjects. In these studies, cyclic variation in abnormal myocardium ranged from 0.9 to 3.1 dB compared with 4.6 to 5.3 dB in normal subjects.[14,15] Thus, blunting of cyclic variation appears to be sensitive in detecting dissimilar types of abnormal myocardium. However, the difference in means between normal and abnormal values was only 2 dB in some studies.[12,13,15] Reproducibility of data acquisition and measurement then become important when considering a clinical setting when interobserver, intraobserver and longitudinal variability take on increasing significance.

There are 2 previous studies of the reproducibility of backscatter in normal subjects. Vered et al[14] repeated measurements of integrated backscatter from digitized 2-dimensional frames (obtained by a single observer) during the entire cardiac cycle. Cyclic variation was 4.2 ± 1.3 dB in the septum and 5.2 ± 1.5 dB in the posterior wall, not significantly different from the values we obtained. In their study, interobserver variability was <1.4 dB and intraobserver variability was <1 dB. Masuyama et al[17] measured cyclic variation of backscatter from M-mode backscatter recordings. Two investigators obtained and measured their own data to determine interobserver variability, calculated as the mean absolute difference. Intraobserver variability was determined by 1 observer repeating analysis of the initial recording. Cyclic backscatter variation was 4.9 ± 1.3 dB in the septum and 6.3 ± 0.8 dB in the posterior wall, the latter similar to the value obtained in our study. Mean inter- and intraobserver variability was ≤1.2 dB and ≤0.8 dB, respectively. Thus, both studies obtained lower variability than we were able to demonstrate.

Our study differs in experimental design from the above-mentioned studies and may explain the higher variability of measurements. First, we investigated the reproducibility of measurements for the entire process of data acquisition, including transducer placement and echocardiographic instrument adjustment. Second, we studied longitudinal reproducibility. Third, we evaluated the reproducibility of measurements in paired 2-dimensional frames, as well as in M-mode recordings.

In our study we sampled only 2 frames per cardiac cycle (2-dimensional studies) and limited "ice pick views" of the myocardium (M-mode images). In the 2-

dimensional studies, we attempted to define end-diastole and end-systole according to standard criteria; however, mechanical end-systole and the backscatter nadir may not be simultaneous, and, therefore, may provide one explanation for the relatively low cyclic change in backscatter in some of the normal subjects. In addition, the use of different points in the cycle for end-systole with the M-mode and 2-dimensional techniques may have introduced variability in the results. Our intention was to identify points in the cardiac cycle that lend themselves readily to a clinical setting and to use them for the measurement of backscatter. While the M-mode method provides for improved temporal sampling throughout the cardiac cycle, the relatively narrow volume interrogated by the beam was limited to essentially 1 site. On the other hand, the 2-dimensional approach we used had limited temporal sampling (i.e., 2 frames), but provided for spatial averaging.

Reducing the variance between repeat examinations of the same person and between observers is tied to the number of independent samples of backscatter making up each measurement. There are a number of ways to increase the number of independent samples making up a determination so that reproducibility can be improved. These include sampling more sites per M-mode determination and more or larger regions of interest per 2-dimensional determination. Another approach is to make use of a waveform derived from M-mode or 2-dimensional backscatter and to match this in a least-mean-square sense against a template.[25,26] By including backscatter data over the entire cardiac cycle, additional site independence is gained via heart motion, and the template provides the means for a determination of cyclic backscatter using the entire cardiac cycle rather than a 2-point difference as was used in this study.

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Effects of Cardiac Transplantation on Ventilatory Response to Exercise

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Patients with heart failure frequently exhibit an excessive ventilatory response to exercise, which is acutely unaltered by therapeutic interventions. To investigate whether these ventilatory responses resolve after cardiac transplantation, 15 ambulatory patients with severe heart failure underwent exercise testing with measurement of respiratory gases before and 1.4 ± 0.6 months after transplantation. Ventilatory response was also measured in 7 age-matched, sedentary control subjects. Left ventricular ejection fraction at rest and hemodynamic measurements were obtained before and after transplantation in all patients. After transplantation, ejection fraction at rest increased from 16 ± 6 to 56 ± 10%, pulmonary capillary wedge pressure declined from 26 ± 8 to 12 ± 5 mm Hg, and cardiac index increased from 1.7 ± 0.5 to 2.8 ± 0.5 liters/min/m^2 (all $p < 0.001$). Peak oxygen consumption increased from 11.8 ± 1.9 to 19.2 ± 3.1 ml/kg/min ($p < 0.001$), but remained significantly lower than that in control subjects (33.4 ± 6.9 ml/kg/min; $p < 0.01$). Minute ventilation ($\dot{V}_E$) was significantly reduced after transplantation, but excessive compared with normal values. Ventilation at a carbon dioxide production of 1 liter/min decreased significantly after cardiac transplantation (52.1 ± 7.9 to 38.8 ± 3.8 liters; $p < 0.01$), but remained elevated when contrasted to that in control subjects (31.4 ± 3.4 liters; $p < 0.05$). Ventilatory response to exercise is significantly improved after cardiac transplantation; however, $\dot{V}_E$ remains excessive. This may reflect an attenuated cardiac output response to exercise, abnormal intrapulmonary pressures or persistent deconditioning.

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Patients with heart failure exhibit an excessive ventilatory response to exercise, which has been related to the sensation of exertional dyspnea. The pathophysiologic basis for this heightened ventilatory response remains unclear. Possible mechanisms include increased work of breathing, chronic fibrotic lung changes, ventilation-perfusion abnormalities, early lactic acidosis, respiratory muscle underperfusion, altered arterial carbon dioxide partial pressure (PCO_2) control of ventilation, or activation of pulmonary juxtacapillary receptors.[1–5] Acute therapeutic interventions with inotropic agents or vasodilators do not alter the ventilatory response to exercise.[6] The impact of chronic therapies, including cardiac transplantation on these ventilation abnormalities, has been poorly defined. Accordingly, we investigated whether the excessive ventilatory response to exercise in patients with heart failure is reversible after cardiac transplantation. Fifteen ambulatory patients with chronic heart failure who underwent cardiac transplantation performed maximal exercise with expired gas analysis before and approximately 1 year after transplantation.

METHODS

Fourteen men and 1 woman (average age 52 ± 11 years, range 32 to 64) undergoing cardiac transplantation were studied. Etiology of heart failure was coronary artery disease in 8 patients, and dilated cardiomyopathy in 7 (Table I). All patients received digoxin, diuretics and angiotensin-converting enzyme inhibitors before transplantation, and prednisone, azathioprine and cyclosporin A after. Exclusion criteria for exercise included severe angina before transplantation, recent allograft rejection or pulmonary infection (<1 month), or evidence of chronic obstructive lung disease on pulmonary function testing. Six men and 1 woman (average age 47 ± 10 years, range 35 to 58) served as control subjects. All subjects were sedentary nonsmokers with a normal medical history, physical exam and electrocardiogram.

Study protocol: Ejection fraction at rest, hemodynamic measurements and exercise testing with measurement of respiratory gases were performed on patients before and 1.4 ± 0.6 months (range 0.75 to 2) after cardiac transplantation. Pulmonary function tests were obtained in all patients before cardiac transplantation. Studies were obtained at the initial evaluation for cardiac transplantation and at the first or second year annual evaluation after transplantation. All control subjects underwent maximal exercise testing with measurement of respiratory gases.

Left ventricular ejection fraction was measured using radionuclide angiography or cardiac catheterization,

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TABLE I Hemodynamic Measurements and Peak Exercise Response in the 15 Patients Before and After Transplantation

Pt.	Age (yr)	Etiology of CHF	Hemodynamic Measurements EF (%)	PCW (mm Hg)	CI (L/min/mm^2)	PVR (Wood Units)
			Before Transplantation			
1	55	CAD	21	27	1.5	3.0
2	48	DC	19	29	1.3	5.0
3	59	CAD	15	16	2.2	1.2
4	50	CAD	21	25	2.1	3.0
5	65	CAD	22	35	1.9	3.4
6	52	DC	19	35	1.8	3.4
7	32	DC	10	25	1.4	4.9
8	63	CAD	24	35	1.5	3.5
9	64	DC	17	15	2.4	2.2
10	58	CAD	4	19	2.5	1.5
11	49	CAD	12	23	1.6	5.7
12	33	DC	20	36	1.9	2.2
13	57	DC	10	28	1.4	5.1
14	60	CAD	20	36	2.0	2.2
15	35	DC	13	7	1.7	3.3
Mean ± SD	52 ± 11		16 ± 6	26 ± 8	1.7 ± 0.5	3.3 ± 1.4
Pt.	Time After Transplantation (yr)					
			After Transplantation			
1	1.0		60	5	2.9	2.4
2	1.0		50	4	2.4	1.5
3	1.0		76	11	2.7	2.0
4	2.0		53	12	3.9	1.2
5	1.0		51	13	2.0	2.4
6	1.0		70	21	2.8	1.3
7	0.75		54	11	2.7	1.5
8	0.75		65	16	2.8	2.2
9	0.83		68	17	3.5	0.4
10	0.75		52	8	2.9	1.2
11	2.0		49	6	2.1	2.3
12	0.83		55	17	2.7	1.8
13	1.0		53	17	2.5	2.6
14	1.8		38	7	2.2	2.0
15	2.0		52	16	3.5	3.8
Mean ± SD	1.4 ± 0.6		56 ± 10*	12 ± 5*	2.8 ± 0.5*	1.9 ± 0.8*

*$p < 0.05$ before versus after transplantation.

CAD = coronary artery disease; CHF = congestive heart failure; CI = cardiac index; DC = dilated cardiomyopathy; EF = ejection fraction; f = respiratory rate; HR = heart rate; Mean BP = mean arterial blood pressure; NA = not achieved; PCW = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RQ = respiratory quotient; V_E = minute ventilation; V_E-VCO_2 1 Liter = minute ventilation at carbon dioxide production of 1 liter; VO_2 = oxygen consumption rate; VO_2 AT = oxygen consumption at anaerobic threshold.

or both. Hemodynamic measurements at rest were determined from Swan-Ganz catheterization performed with patients on their chronic medical regimens. Cardiac output was measured by thermodilution. Spirometry was performed using standard techniques. Lung volumes, flow rates and diffusing capacity were measured.

Maximal treadmill exercise testing with respiratory gases was performed in all subjects using the modified Naughton protocol. Exercise work loads were of 3-minute duration. Heart rate was monitored continuously throughout exercise testing. Blood pressure was measured by cuff at rest and during the last minute of each work load. Measurements of mixed expired oxygen and carbon dioxide, and expired volume were determined at rest and every 15 seconds throughout exercise using a metabolic cart (Sensor-Medics, Anaheim, California). The anaerobic threshold was defined as the point at which the ventilatory equivalent for oxygen was minimal followed by a progressive increase, while the ventilatory equivalent for carbon dioxide (CO_2) remained unchanged.

Ventilation was assessed by correlation of minute ventilation ($\dot{V}_E$) with minute CO_2 production (VCO_2). In control subjects and in patients with heart failure, VCO_2 is the primary metabolic stimulus for $\dot{V}_E$. A linear increase in $\dot{V}_E$ with VCO_2 occurs, so that arterial PCO_2 remains constant. However, in patients with heart failure, $\dot{V}_E$ at any given VCO_2 is higher than normal. Therefore, to contrast $\dot{V}_E$ between subjects, it was correlated with VCO_2. From the linear regression analysis, $\dot{V}_E$ at VCO_2 of 1 liter/min ($\dot{V}_E$-VCO_2 1 liter) was derived in each subject and used as a quantitative index of ventilatory drive.[6]

Statistical analysis: Statistical analysis was performed using Student's *t* test for paired or nonpaired testing, as appropriate. Analysis of variance was used for multiple group comparisons. Linear regression analysis was performed using the least-squared method. A

TABLE I (Continued)

	Peak Exercise Response							
Pt.	HR (beats/min)	Mean BP (mm Hg)	$\dot{V}_E$ (L/min)	f (breaths/min)	RQ	VO_2 AT (ml/kg/min)	Peak VO_2 (ml/kg/min)	$\dot{V}_E$-VCO_2 1 Liter
				Before Transplantation				
1	147	117	46.0	28.0	0.96	11.5	14.0	35
2	135	117	31.1	35.2	0.98	10.6	11.3	50
3	140	93	29.2	40.7	0.90	7.9	9.1	50
4	110	93	41.7	31.9	1.04	10.5	12.0	52
5	115	125	47.8	35.2	0.97	10.4	12.7	57
6	136	77	57.3	46.5	1.07	9.6	13.9	51
7	122	85	30.7	44.7	0.96	10.7	14.0	62
8	110	78	39.1	29.2	1.21	6.6	10.3	49
9	130	63	44.1	21.4	1.01	6.8	10.2	57
10	156	97	29.4	24.6	0.79	8.7	11.1	39
11	119	67	44.2	34.0	0.97	6.5	10.0	68
12	142	120	34.8	29.6	0.82	8.7	13.5	47
13	120	90	57.8	29.6	0.94	10.6	14.4	60
14	108	97	35.5	52.0	0.74	9.3	10.8	67
15	162	80	28.2	23.4	0.77	NA	9.0	38
Mean ± SD	130 ± 17	93 ± 19	39.8 ± 9.8	33.7 ± 8.9	0.92 ± 0.15	9.2 ± 1.7	11.8 ± 1.9	52 ± 10
Pt.	Time After Transplantation (yr)							
				After Transplantation				
1	115	117	55.0	27.8	0.98	14.6	18.9	36
2	156	140	44.6	33.0	1.05	13.5	17.3	42
3	150	117	46.1	42.7	1.02	11.3	15.6	36
4	170	140	58.3	31.1	1.11	16.7	24.3	33
5	139	115	54.0	35.4	1.02	11.8	17.9	42
6	150	105	43.7	38.7	1.03	12.5	13.6	44
7	125	105	40.5	35.1	1.09	13.0	16.1	39
8	175	95	60.9	33.6	1.05	17.5	24.4	36
9	160	117	77.1	35.5	1.10	13.6	22.2	37
10	115	103	88.0	33.5	1.16	12.2	20.6	40
11	97	107	54.0	29.1	1.03	11.8	19.3	36
12	178	110	50.9	29.4	0.96	15.8	18.4	34
13	129	97	64.6	28.2	1.03	14.1	19.0	42
14	143	133	75.0	41.0	1.04	11.5	18.9	46
15	170	94	100.1	36.5	1.11	14.7	20.8	40
Mean ± SD	144 ± 25	113 ± 15*	60.9 ± 17.3*	34.0 ± 4.5	1.04 ± 0.06*	13.6 ± 2.0*	19.2 ± 3.2*	39 ± 4*

p value <0.05 was considered statistically significant. Data are presented as mean ± standard deviation.

RESULTS

Hemodynamic measurements at rest (Figure 1 and Table I): After transplantation, left ventricular ejection fraction and cardiac index increased from 16 ± 6 to 56 ± 10% and from 1.7 ± 0.5 to 2.8 ± 0.5 liters/min/m^2, respectively. Pulmonary capillary wedge pressure and vascular resistance decreased from 26 ± 8 to 12 ± 5 mm Hg and from 3.3 ± 1.4 to 1.9 ± 0.8 Wood Units, respectively ($p < 0.05$).

Pulmonary function tests (Table II): Patients tended to have a mildly reduced forced vital capacity and expiratory volume in 1 second with a normal ratio. Maximal voluntary ventilation, as well as maximal inspiratory and expiratory pressures, tended to be low, suggesting respiratory muscle weakness. Diffusing capacity was also mildly decreased.

Exercise testing (Tables I and III; Figures 2 to 5): Exercise was limited owing to fatigue in all control subjects. Six patients were limited by dyspnea before versus 4 after cardiac transplantation (p = not significant).

Heart rate at rest was significantly higher and maximal heart rate significantly lower in patients before and after transplantation than in control subjects. Mean arterial pressure was significantly decreased in patients with heart failure both at rest and with maximal exercise (Table III). In patients after transplantation, blood pressure at rest tended to be increased ($p < 0.06$ vs control subjects) and did not increase significantly with exercise.

After transplantation, exercise duration increased significantly, but remained less than normal. Similarly, peak oxygen consumption increased from 11.8 ± 1.9 to 19.2 ± 3.1 ml/kg/min ($p < 0.01$), but remained reduced when compared with that of control subjects. Oxygen consumption at the anaerobic threshold increased from 9.2 ± 1.7 to 13.6 ± 2.0 ml/kg/min after transplantation ($p < 0.01$) (Figure 2).

Peak $\dot{V}_E$ increased significantly after transplantation owing to attainment of higher work loads, but remained

TABLE II Pulmonary Function Tests in Patients Before Transplantation

	Actual Value	% of Predicted Value
Forced vital capacity (L)	3.34 ± 0.89	73 ± 27
FEV1 (L)	2.78 ± 0.92	79 ± 20
FEV1/FVC (%)	78 ± 11	
Maximum voluntary ventilation (L/min)	119 ± 37	81 ± 23
Diffusing capacity (ml/min/torr)	21 ± 6	78 ± 17
Maximum inspiratory pressure (torr)	57 ± 23	
Maximum expiratory pressure (torr)	97 ± 27	

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

significantly less than normal. Maximal respiratory rate was comparable between all groups. Therefore, peak tidal volume was significantly greater in patients after transplantation and in normal subjects than in those before transplantation (Figure 3).

To compare the groups at matched submaximal work loads, ventilatory data from 3 and 6 minutes of exercise were analyzed. Resting and submaximal oxygen consumption, and VCO_2 were similar in all groups. Submaximal $\dot{V}_E$, respiratory rate and the ventilatory equivalent for VCO_2 were significantly reduced after cardiac transplantation. However, the ventilatory equivalent for VCO_2 and $\dot{V}_E$ remained abnormal (Figure 3).

In all subjects $\dot{V}_E$ was linearly related to VCO_2 ($r \geq 0.90$; $p < 0.01$). The average slope of this relation was significantly higher in patients with heart failure than in those after transplantation and in control subjects. Thus, after transplantation, this excessive ventilatory response attenuated, but remained abnormal (Figure 4). Using the linear regression equation derived in each subject, $\dot{V}_E$ for VCO_2 of 1 liter ($\dot{V}_E$-VCO_2 1 liter) was calculated. This provided a quantitative index of ventilatory drive at a comparable point. $\dot{V}_E$-VCO_2 1 liter was significantly reduced after transplantation, although it remained excessive when compared with that of control subjects (Figure 5).

DISCUSSION

Exertional dyspnea is a frequently limiting symptom in patients with heart failure. Because dyspnea is a sensation, it is difficult to quantify. Psychological scoring scales and measurement of $\dot{V}_E$ have been used to provide objective correlates of dyspnea. In this study we investigated the reversibility of this excessive ventilatory response after cardiac transplantation. Although several prior studies described the exercise response after cardiac transplantation,[7-13] our study is the first longitudinal investigation of exercise performance in a group of patients before and after cardiac transplantation. As an impaired skeletal muscle vasodilatory response has been shown to be present initially after transplantation,[14] and as skeletal muscle atrophy and deconditioning are likely

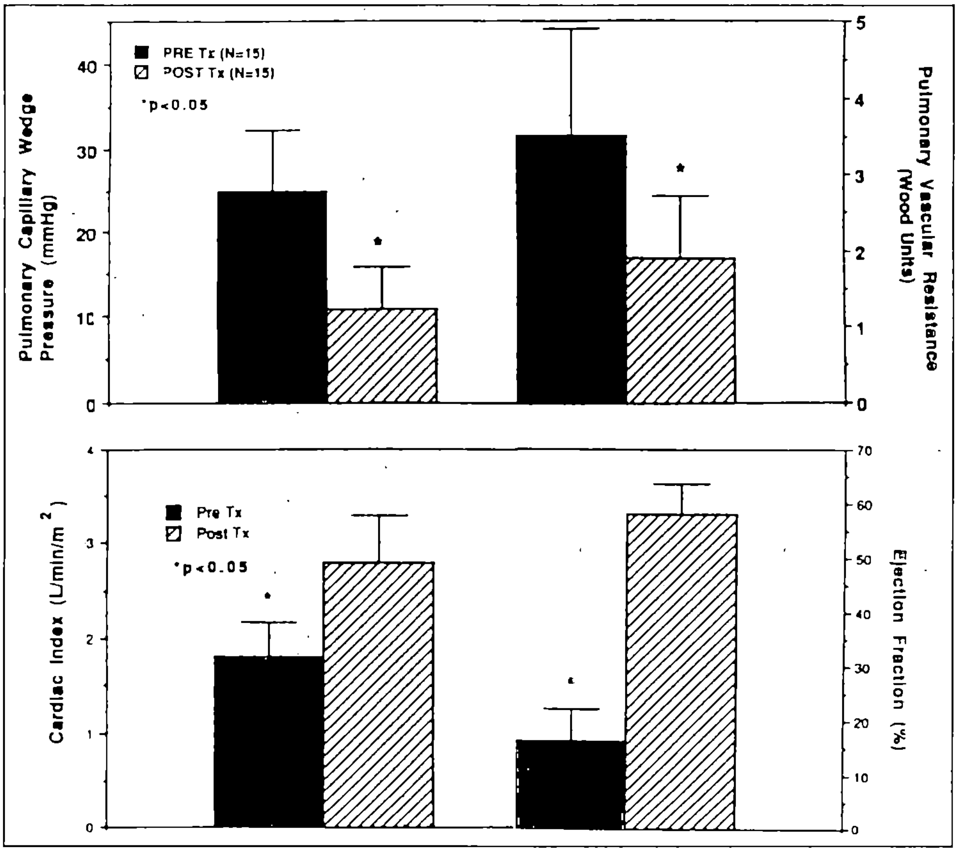

FIGURE 1. Hemodynamic measurements and left ventricular ejection fraction at rest before (PRE) and after (POST) cardiac transplantation (Tx).

to be most prominent in the initial postoperative period, repeat exercise tests in our study were performed approximately 1 year after transplantation.

Cardiac transplantation prolongs survival and enhances the quality of life in patients with end-stage heart failure. However, a recent study suggests that minimal improvement occurs in peak exercise capacity in ambulatory heart failure patients after transplantation.[15] That study compared patients after transplantation with "medically stabilized" ambulatory heart failure subjects. In contrast, our study demonstrates a dramatic improvement in exercise duration and peak oxygen consumption, as well as a delay in the onset of the anaerobic threshold in all patients. Selection criteria used in our institution limits cardiac transplantation to those ambulatory subjects with a markedly reduced peak oxygen consumption.[16] In these ambulatory heart failure patients, exercise capacity is clearly enhanced by transplantation.

Few prior studies have evaluated abnormalities in pulmonary function and ventilatory responses before and after cardiac transplantation. Hosenspud et al[17] compared spirometric results before and after transplantation, and noted improvements in forced vital capacity and expiratory volume at 1 second after transplantation. The reduction in lung volumes before transplantation was largely attributed to cardiomegaly, interstial edema and pleural effusions. Although our patients did not have pulmonary function tests after transplantation, spirometric results before transplantation were similar and revealed mildly reduced lung volumes. Reduced maximal inspiratory and expiratory pressures were also found, suggesting respiratory muscle weakness.

The chronotropic response to exercise of the denervated heart has been well-described.[18] Similar to prior studies, we demonstrated a resting tachycardia and attenuated maximal heart rate response to exercise in patients after transplantation compared with those in normal subjects. Reduced peak oxygen consumption and early onset of the anaerobic threshold weres also observed, and are consistent with prior observations.[7] This impaired peak exercise capacity in patients after transplantation is most likely secondary to an attenuated cardiac output response by the denervated heart.

TABLE III Cardiovascular Response to Exercise

	Normal (n = 7)	Before Transplantation (n = 15)	After Transplantation (n = 15)
Exercise duration (min)	27.4 ± 6.4	6.7 ± 3.3*†	15.8 ± 4.3*
Heart rate (beats/min)			
Rest	79 ± 3	96 ± 15*	102 ± 17*
Maximum exercise	170 ± 16	130 ± 17*	144 ± 25*
Mean blood pressure (mm Hg)			
Rest	95 ± 19	86 ± 14*†	110 ± 14
Maximum exercise	118 ± 16	93 ± 19*†	113 ± 15
Oxygen consumption (ml/kg/min)			
Rest	4.8 ± 1.5	4.8 ± 0.9	4.7 ± 0.7
Anaerobic threshold	21.0 ± 2.7	9.2 ± 1.7*†	13.6 ± 2.0*
Maximum exercise	33.4 ± 6.9	11.8 ± 1.9*†	19.2 ± 3.2*
Respiratory quotient			
Rest	0.84 ± 0.04	0.81 ± 0.12	0.82 ± 0.08
Maximum exercise	1.08 ± 0.07	0.92 ± 0.15*†	1.04 ± 0.06

*p <0.05 versus normal; †p < 0.05 before versus after transplantation.

An abnormal blood pressure response to exercise was described in patients after transplantation. Mean arterial blood pressure at rest tended to be elevated, probably due to cyclosporine therapy. With exercise, no significant increase occurred. The cause of this blunted blood pressure response is unclear.

The ventilatory response to exercise after transplantation is less well-characterized. Conflicting results have been reported. Banner et al[8] and Theodore et al[13] described a normal ventilatory response, whereas Savin et

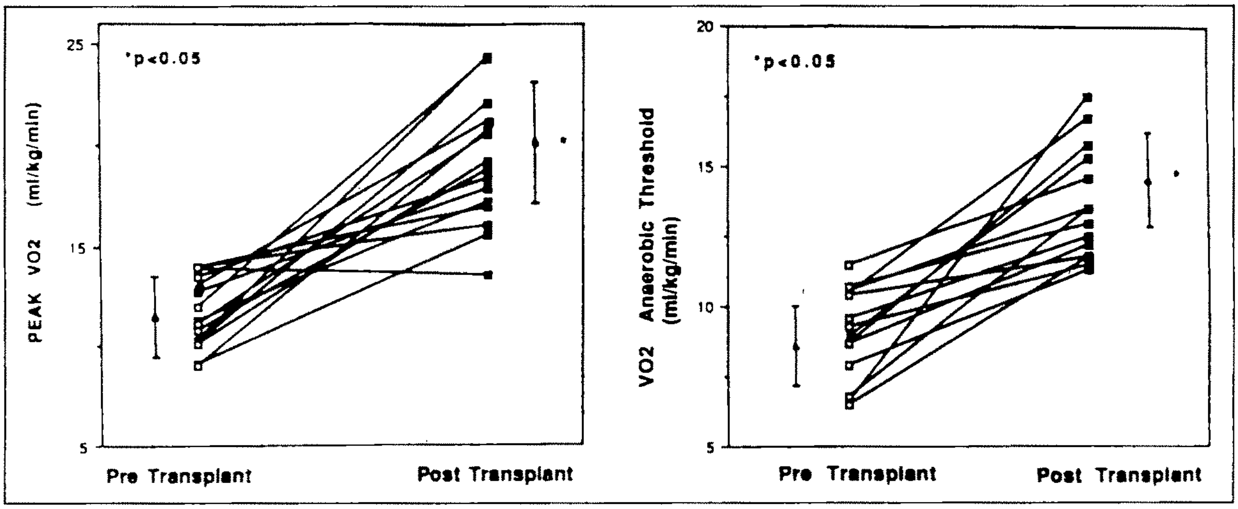

FIGURE 2. Peak exercise oxygen consumption (VO2) and oxygen consumption at the anaerobic threshold in 15 patients before (Pre) and after (Post) cardiac transplantation.

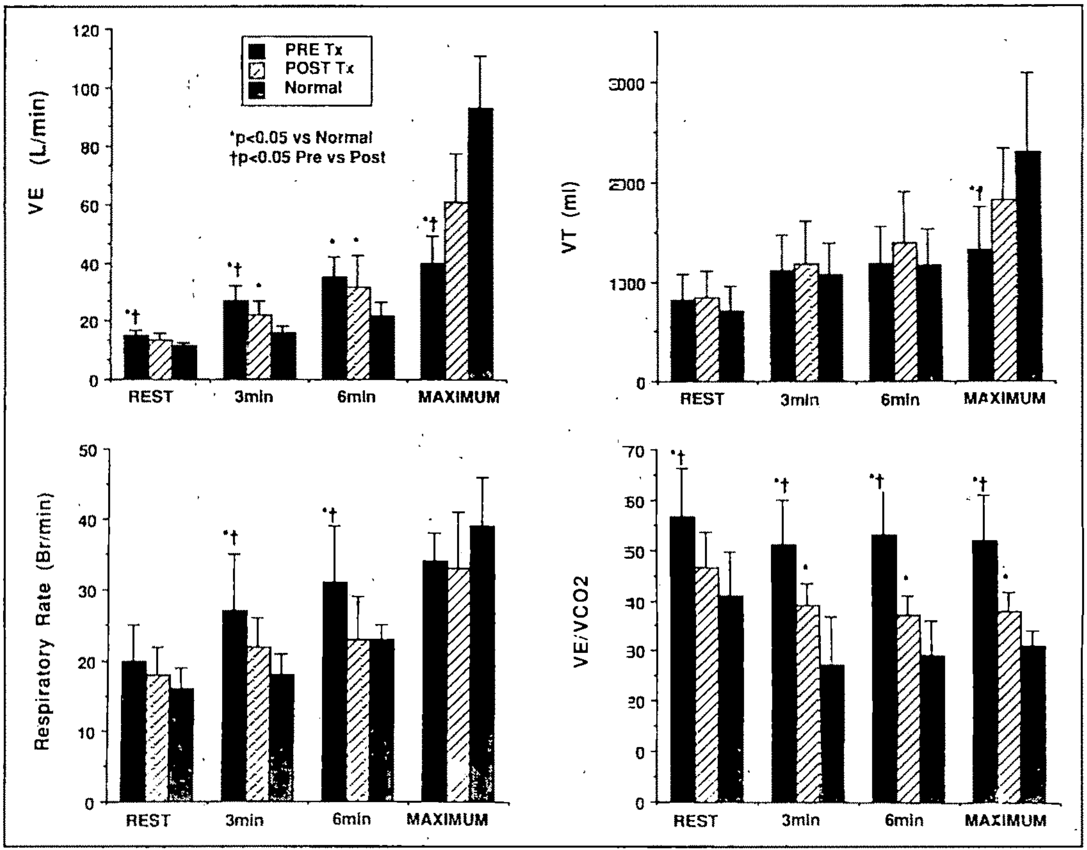

FIGURE 3. Minute ventilation (VE), tidal volume (VT), respiratory rate and ventilatory equivalent for carbon dioxide production (VE/VCO2) at rest, and at submaximal and peak exercise *(from left to right)* in patients before (PRE) and after (POST) transplantation (Tx), and in normal subjects.

al[7] noted persistent excessive $\dot{V}_E$ after transplantation. None of these studies used patients as their own controls. All used varying exercise protocols. Our longitudinal study helps to clarify the impact of cardiac transplantation on ventilatory abnormalities. In our study, the excessive ventilatory response to exercise in patients with heart failure was significantly attenuated in the first year after transplantation, but remained excessive when compared with that of control subjects.

Our analysis was performed using absolute quantitation of $\dot{V}_E$ at each work load, and linear regression analyses with VCO_2. In control subjects, $\dot{V}_E$ increases lin-

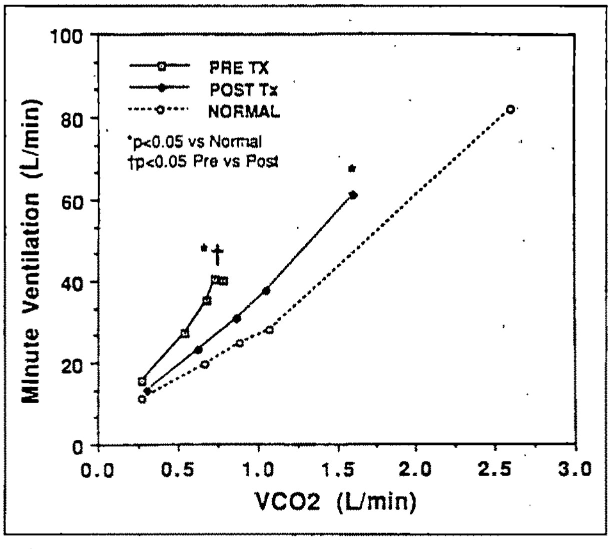

FIGURE 4. Linear regression analysis of minute ventilation versus carbon dioxide production (VCO2) in patients before (PRE) and after (POST) transplantation (Tx), and in normal subjects.

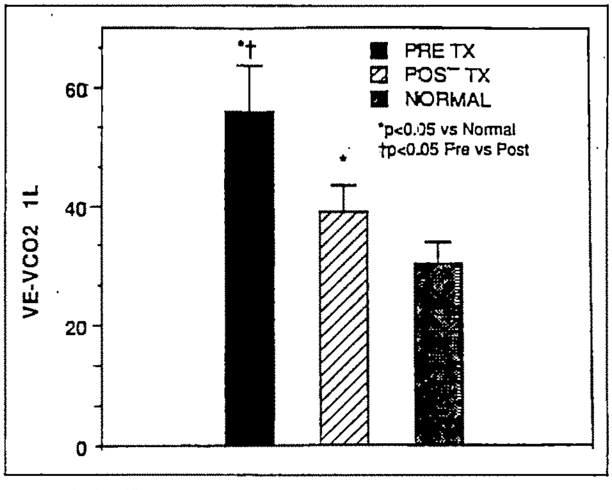

FIGURE 5. Histograms of the ventilatory equivalent for carbon dioxide production per minute at 1 liter (VE-VCO2 1L) *(from left to right)* in patients before (PRE) and after (POST) transplantation (TX), and in normal subjects.

early with VCO_2 so that arterial PCO_2 remains constant. In patients with heart failure, $\dot{V}_E$ also increases linearly with VCO_2; however, this relation is shifted upward at rest and throughout exercise. Using the relation of $\dot{V}_E$ to VCO_2 we again demonstrated an excessive ventilatory response in patients with heart failure. After transplantation, the response was ameliorated but remained abnormal.

The mechanism of the abnormal ventilatory response before and after transplantation remains unclear. Previous studies in subjects with heart failure and after cardiac transplantation suggest that these ventilatory abnormalities are unrelated to changes in arterial CO_2 pressure, hypoxia or lactate production.[1,19] Pulmonary receptors are also not likely to be the major etiologic factor, because the ventilatory response to exercise of heart-lung transplant recipients is similar to that of cardiac transplant recipients.[8] Moreover, the sensation of dyspnea is still experienced in heart-lung transplant patients despite pulmonary denervation.[8]

A potential mechanism for the excessive ventilatory response may be an attenuated cardiac output response to exercise in patients before transplantation owing to left ventricular dysfunction,[6] and after owing to cardiac denervation.[12,20] In heart failure, Sullivan et al[1] suggested that the excessive ventilatory response resulted from an abnormal increase in physiologic dead space due to dynamic ventilation perfusion abnormalities from an attenuated cardiac output response. Similarly, in patients after transplantation, pulmonary hypoperfusion during exercise may occur. Of note, the ventilatory equivalent at rest for VCO_2 is normal after transplantation, as resting cardiac output is near normal.

Another explanation for the excessive $\dot{V}_E$ is respiratory muscle dysfunction in patients before and after transplantation. The respiratory muscles may be key modulators of the sensation of dyspnea.[21] Respiratory muscle weakness and underperfusion may result in muscle fatigue and thus dyspnea. Using near-infrared spectroscopy, we recently demonstrated accessory respiratory muscle deoxygenation in patients with heart failure during exercise.[5]

Lastly, the mechanism for excessive ventilatory responses in patients before and after transplantation may be divergent. Physical training can significantly improve the ventilatory response to exercise in patients before and after transplantation and in normal subjects.[9,22] Because the response after transplantation is near normal, it may be that the observed abnormalities are simply due to deconditioning.

The present study is limited in that it is descriptive. Therefore we can only speculate on potential mechanisms for the abnormal ventilatory responses in patients before and after transplantation.

Clinically, this study is important in that it provides the first longitudinal description of the cardiopulmonary response to exercise in ambulatory patients before and after transplantation. Overall exercise performance is greatly enhanced. Although ventilatory changes persist after transplantation, they are markedly attenuated.

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Influence of Residual Blood Flow in the Infarct-Related Artery on Ventricular Tachycardia After Myocardial Infarction

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Ventricular tachycardia (VT) late after myocardial infarction is generally attributed to reentry due to slowed conduction and heterogeneous refractoriness in surviving myocytes bordering and traversing the infarcted area.[1] Thrombolytic trials and angiographic studies indicate that a patent infarct-related artery (IRA) is associated with lower sudden death mortality and that this benefit may be independent of measurable preservation of global left ventricular function.[2-5] Similarly, the presence of coronary collateral circulation to nonreperfused IRAs is associated with a reduction in infarct size, and a decrease in early ventricular arrhythmias.[6-8] Predictors of VT development after myocardial infarction including inducible arrhythmias at programmed electrical stimulation,[9-11] development of a left ventricular aneurysm and late potentials detected by signal-averaged electrocardiography[12,13] are also favorably influenced by IRA perfusion. To determine if absence of residual IRA flow distinguishes post–myocardial infarction patients with VT, we reviewed coronary angiograms of 14 patients with recurrent VT late after myocardial infarction and 14 matched control patients.

Fourteen consecutive patients admitted to UCLA Medical Center for treatment of spontaneous sustained VT occurring in the absence of recurrent acute infarction were matched with 14 control patients having no history of ventricular arrhythmias. All patients with VT underwent coronary arteriography during the hospitalization for VT. Patients were excluded if they had a history of myocardial infarction within 6 months, prior coronary bypass surgery or coronary angioplasty. Study patients were matched for age, sex, location of prior infarction, IRA and ejection fraction. In addition to documented spontaneous episodes of VT, all study patients underwent electrophysiologic studies documenting sustained monomorphic VT defined as an induced ventricular rhythm at a rate >100 beats/min that displayed consistent beat-to-beat QRS morphology and lasting >29 seconds or requiring an intervention for termination.

Each cardiac angiogram was analyzed by 4 angiographers. Left ventricular ejection fractions were calculated by the planimetry method from left ventriculograms obtained in the 30° right anterior oblique projection. Infarction location was identified by the presence of regional asynergy or dysynergy on biplane ventriculography in correlation with the clinical history and electrocardiogram. Four angiographers unaware of the clinical history performed analyses of coronary arteriograms. Anterograde flow in the IRA was graded as: grade 0 or 1, no or minimal anterograde perfusion; grade 2 or 3, partial or complete anterograde perfusion.[5]

A coronary collateral vessel was considered present if anterograde IRA flow was less than Thrombolysis in Myocardial Infarction trial grade 2 and visible collateral vessels provided opacification of the distal IRA which measured >1.0 mm in diameter.[14]

The clinical characteristics of the 14 study and 14 matched control patients are listed in Table I. No significant differences with respect to age, sex, extent of coronary artery disease or left ventricular function were present between the 2 groups. Left ventricular ejection fraction was markedly depressed in both groups. The IRA was the right coronary in 5 patients and left anterior descending artery in 6. No patient had a circumflex artery identified as the sole infarction vessel. Three patients had 2 prior infarctions. The degree of anterograde flow in the IRA and the presence of collateral flow to those IRAs having minimal or no anterograde perfusion is listed in Table II. A total of 17 IRAs were identified in each group. Anterograde IRA perfusion was observed less frequently in patients with VT than in control patients (41 vs 76%, $p < 0.04$*). Collateral filling of IRAs having grade 0 or 1 anterograde flow was seen in 1 of ten subjects (10%) with VT compared with 4 of 4 control subjects (100%)* ($p > 0.004$).

Our findings demonstrate that residual blood flow to the IRA either from recanalization or collaterals occurs

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TABLE I Clinical Characteristics

	VT	Matched Controls	p Value
Age (yr ± SD)	62 ± 8	60 ± 12	NS
Sex (men)	12	9	NS
Ejection fraction (mean ± SD)	0.30 ± 0.12	0.30 ± 0.09	
Extent of CAD			
1-vessel	3	6	NS
2-vessel	3	5	NS
3-vessel	8	3	NS
Right	5	5	NS
LAD	6	6	
LC	0	0	
LAD + right	2	2	
LAD + LC	1	1	

CAD = coronary artery disease, LAD = left anterior descending artery; LC = left circumflex artery; NS = not significant; VT = ventricular tachycardia.

TABLE II Infarct-Related Artery Flow and Collateral Circulation

	Infarct Arteries	TIMI 0–1	Collateral Vessels	TIMI 2–3
VT	17	10 (59%)	1 (10%)	7 (41%)
Control	17	4 (24%)	4 (100%)	13 (76%)
p Value		<0.04	<0.004	<0.04

TIMI = Thrombolysis in Myocardial Infarction trial; VT = ventricular tachycardia.

less frequently in patients having VT late after myocardial infarction than in patients with similar size infarctions and severity of coronary artery disease but without VT. Several other studies also suggest that preserved IRA flow confers protection against the development of VT.[9-13] When programmed stimulation is performed within 1 month after myocardial infarction, patients who receive a thrombolytic agent are less likely to have inducible VT then are those in whom acute reperfusion was not achieved.[9-11] Lange et al[13] obtained signal-averaged electrocardiograms in 109 patients who underwent catheterization within 24 months after a first myocardial infarction and reported a higher incidence of late potentials in patients without residual IRA flow. In an earlier report,[4] these investigators found an 18% incidence of sudden death and a greater total mortality among 115 patients without residual IRA flow compared with no sudden deaths in a matched group with patent IRAs. The lack of coronary collateral formation in patients with VT may also contribute to arrhythmia risk. Further study is needed to determine how residual perfusion protects against the development of the VT substrate.

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Prevalence of Silent Myocardial Ischemia Detected by 24-Hour Ambulatory Electrocardiography, and Its Association with New Coronary Events at 40-Month Follow-Up in Elderly Diabetic and Nondiabetic Patients with Coronary Artery Disease

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Patients with diabetes mellitus have a higher prevalence and incidence of coronary artery disease (CAD) than nondiabetic patients. The prevalence of silent myocardial ischemia was found to be increased in diabetic patients by some investigators,[1,2] but not by others.[3,4] We report the results from a prospective study determining the prevalence of silent myocardial ischemia and the incidence of new coronary events associated with silent ischemia in diabetic and nondiabetic patients with CAD.

In a prospective study of 1,489 elderly patients in a long-term health care facility, CAD was diagnosed in 157 of 310 diabetics (51%) and in 442 of 1,179 nondiabetics (37%; $p < 0.001$) (Table I). CAD was diagnosed if the patient had a documented clinical history of myocardial infarction or electrocardiographic evidence of Q-wave myocardial infarction (580 patients), or typical angina pectoris without previous myocardial infarction (19).

Ambulatory electrocardiographic monitoring was performed for 24 hours using portable Avionics tape recorders (model 445) to obtain 2 leads corresponding to a modified V_1 and V_5 in the 599 elderly patients with CAD. The tapes were analyzed using a CardioData Mk 3 computer system. ST-segment changes were written out on electrocardiographic paper at a speed of 25 mm/s and interpreted by 2 cardiologists. Patients with marked ST-segment depression at rest (≥ 1.5 mm) were excluded from the study. Silent ischemia was diagnosed if horizontal or downsloping ST-segment depression ≥ 1 mm below the level at rest occurred at 80 ms after the J point, lasted for ≥ 1 minute and was unassociated with anginal symptoms. If ST-segment depression at rest occurred, an additional 2 mm of ischemic ST-segment depression below the resting level at 80 ms after the J point was needed.

Table I shows the prevalence of men and women with CAD, of technically adequate 24-hour ambulatory electrocardiograms and of silent myocardial ischemia, and the mean age and follow-up of diabetic and nondiabetic

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TABLE I Prevalence of Coronary Artery Disease in Diabetic and Nondiabetic Patients, and Baseline Characteristics of Elderly Diabetic and Nondiabetic Patients with Coronary Artery Disease

	Diabetics	Nondiabetics	p Value
CAD	157/310 (51%)	442/1,179 (37%)	<0.001
Men with CAD	42/157 (27%)	159/442 (36%)	<0.05
Women with CAD	115/157 (73%)	283/442 (64%)	<0.05
Adequate ambulatory electrocardiogram	136/157 (87%)	365/442 (83%)	NS
Silent ischemia	52/136 (38%)	120/365 (33%)	NS
Age of patients with CAD (yr)	80 ± 8 (62–96)	83 ± 7 (62–101)	<0.001
Follow-up of patients with CAD (mos)	39 ± 23 (3–72)	40 ± 19 (3–75)	NS

CAD = coronary artery disease; NS = not significant.

TABLE II Incidence of New Coronary Events in Elderly Diabetic and Nondiabetic Patients with Coronary Artery Disease With and Without Silent Ischemia

	New Coronary Events		
	Diabetics No. (%)	Nondiabetics No. (%)	p Value
Silent myocardial ischemia	45/52 (87)*	99/120 (83)*	NS
No silent ischemia	43/84 (51)	110/245 (45)	NS
No satisfactory ambulatory electrocardiogram	13/21 (62)	43/77 (56)	NS
All patients	101/157 (64)	252/442 (57)	NS

*$p < 0.001$, comparing silent ischemia with no silent ischemia.
NS = not significant.

patients with CAD. Table I also lists levels of statistical significance. In patients with CAD, silent ischemia was present in 6 of 20 (30%) diabetics and in 6 of 24 (25%) nondiabetics aged 62 to 70 years (p = not significant [NS]), in 17 of 46 (37%) diabetics and in 31 of 101 (31%) nondiabetics aged 71 to 80 years (p = NS), in 25 of 62 (40%) diabetics and in 67 of 191 (35%) nondiabetics aged 81 to 90 years (p = NS), and in 4 of 8 (50%) diabetics and in 16 of 49 (33%) nondiabetics aged >90 years (p = NS).

New coronary events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation or sudden coronary death. Myocardial infarction was documented as previously described.[5] Sudden coronary death was defined as an unexpected cardiac death occurring in a patient with CAD within 1 hour of being clinically stable.[6] Chi-square analyses were used to analyze data.

Table II shows the incidence of new coronary events in diabetics and nondiabetics with CAD in patients with silent ischemia, no silent ischemia, no technically satisfactory 24-hour ambulatory electrocardiogram, and in all patients. The sensitivity and specificity of silent myocardial ischemia diagnosed by 24-hour ambulatory electrocardiogram in predicting new coronary events in elderly patients with CAD were 48 and 86%, respectively.

The prevalence of silent myocardial ischemia detected by exercise thallium scintigraphy,[1] or ambulatory electrocardiographic monitoring and exercise stress testing[2] was found to be higher in diabetic patients with CAD than in nondiabetics with CAD. However, Chipkin et al[3] and Callaham et al[4] observed that the prevalence of silent ischemia detected by exercise stress testing was similar between their diabetic and nondiabetic patients. Callaham et al[4] also demonstrated that the mortality rate in their study was significantly greater in patients with abnormal ST-segment depression than in those without ST-segment changes. Presence or absence of angina pectoris during exercise testing was not related to death.

In our prospective study, the prevalence of CAD was significantly higher in elderly diabetic patients than in elderly nondiabetics. However, the prevalence of silent myocardial ischemia was not significantly different between elderly diabetic and nondiabetic patients with CAD.

Silent myocardial ischemia detected by ambulatory electrocardiography in patients with unstable angina pectoris,[7,8] in high-risk postinfarction patients,[9] or in those with prior myocardial infarction[10,11] or with stable angina pectoris[12,13] is associated with an increased incidence of cardiovascular morbidity and mortality. In our study, both diabetic and nondiabetic patients with CAD had a higher incidence of new coronary events if silent ischemia was present than if it was absent. However, the incidence of new coronary events was not significantly different in diabetic patients with CAD than in nondiabetics with CAD with silent myocardial ischemia, no silent ischemia, no technically adequate 24-hour ambulatory electrocardiogram, or in all patients.

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Frequency of Ventricular Ectopic Activity in Isolated Systolic Systemic Hypertension

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Most studies on the relation between ventricular ectopic activity and hypertension have been performed in patients with diastolic hypertension. There are no data on the prevalence or characteristics of ventricular ectopic activity in patients with isolated systolic hypertension.[1–9] We performed 24-hour ambulatory electrocardiography in 238 patients with isolated systolic hypertension who participated in the Systolic Hypertension in the Elderly Program (SHEP), and in a group of 100 age- and sex-matched normotensive control subjects.[10]

Patients with isolated systolic hypertension were recruited at 3 of 16 SHEP clinical centers (Emory University, University of California at Davis, and the University of Medicine & Dentistry of New Jersey–Robert Wood Johnson Medical School). SHEP is a long-term multicenter randomized placebo-controlled clinical trial to test the efficacy of antihypertensive drug treatment in persons with isolated systolic hypertension aged ≥ 60 years. The criteria for enrollment in SHEP have been published elsewhere.[10] *Men and women aged ≥ 60 years with systolic blood pressure (BP) of 160 to 219 mm Hg and diastolic BP <90 mm Hg were eligible for the study. Baseline BP was obtained using random zero manometers by nurses certified in this technique. Two readings at 2 baseline visits were averaged (4 readings) to obtain baseline BP.*

Electrocardiographic exclusion criteria were atrial fibrillation or flutter, atrioventricular block, multifocal ventricular premature contractions or bradycardia <50 beats/min on the 12-lead electrocardiogram. Normotensive control subjects were selected from those who were potential candidates for SHEP, but did not meet enrollment criteria because they were normotensive (diastolic BP <90 mm Hg and systolic BP <140 mm Hg).

Twenty-four-hour ambulatory electrocardiographic recordings were obtained at baseline before medication was begun. Recordings were obtained using 2-channel reel-to-reel electrocardiographic recorders (DelMar Avionics, Electrocardiocorder model 445). Tapes were analyzed in a blind fashion at a central laboratory by an experienced nurse and 1 physician reader using a computer-based operator-interactive system (DelMar Avionics Trendsetter II, model 900A Dynamic Electrocardioscanner). Arrhythmias were validated independently from rhythm strips recorded at a paper speed of 25 mm/s.[11]

Recorded parameters included total number of ventricular premature contractions per 24 hours, total number of ventricular premature contraction pairs per 24 hours and total number of nonsustained ventricular tachycardia (≥ 3 consecutive ventricular premature contractions) episodes. Age, sex, smoking habits, ethanol consumption, presence or absence of diabetes or congestive heart failure, or both, systolic and diastolic BP, presence of coronary artery disease (defined as evidence of myocardial infarction on the 12-lead electrocardiogram, history of coronary artery bypass surgery, or presence of angina on the Rose questionnaire), serum potassium and left ventricular mass (in a subset of patients) were recorded.

Left ventricular mass was calculated from M-mode hard copy tracings oriented using 2-dimensional echo guidance. Left ventricular mass was calculated using the formula: left ventricular mass = {1.04 ([left ventricular internal diameter + posterior wall thickness + interventricular septal thickness]^3 − [left ventricular internal diameter]^3)} − 13.6 g.[12] *Left ventricular mass was corrected for height and gender as proposed by Levy et al.*[13] *Left ventricular hypertrophy was defined as left ventricular mass >163 g/m for men and 121 g/m in women.*[13] *Because of technical difficulties good quality echocardiograms were obtained only in 39% of the patients (38 normal control subjects and 95 patients with isolated systolic hypertension).*

The logarithm (total number of ventricular contractions premature per 24 hours plus 1) was computed. The data were entered into an IBM AT computer and analyzed using the Statistical Analysis System software (SAS Institute, Cary, North Carolina).

Baseline characteristics of the SHEP and control groups are presented in Table I. Compared with normotensive control subjects, patients with isolated systolic hypertension had greater weight, body mass index, systolic and diastolic BP and were older by 2 years.

Table II and Figure 1 describe the arrhythmias recorded in patients with isolated systolic hypertension and in normotensive control subjects. Patients with isolated systolic hypertension had more ventricular premature contractions (412 ± 1,612/24 hours) than normotensive controls (179 ± 479/24 hours, $p <0.048$). Sixty-seven percent of the patients with isolated systolic hypertension and 52% of normal subjects had >10 ventricular premature contractions per 24 hours ($p = 0.009$).

In isolated systolic hypertension, the number of ventricular premature contractions correlated with age ($r = 0.218, p = 0.002$), male gender ($r = 0.220, p <0.001$) and coronary artery disease ($r = 0.148$, $p = 0.028$). The number of ventricular premature contraction pairs was also related to age ($r = 0.206$, $p = 0.003$), and male

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gender ($r = 0.191$, $p = 0.007$) (Figure 2). Body weight was positively related ($p < 0.0001$) to both left ventricular mass and left ventricular mass corrected for height ($p < 0.004$) but not to ventricular ectopic activity. A relation between left ventricular mass and ventricular ectopic activity was seen for pairs ($p < 0.003$) and ventricular premature contractions ($p < 0.092$) in the SHEP group and for pairs ($p < 0.002$) and for ventricular premature contractions ($p < 0.04$) in the total cohort. A relation between baseline serum potassium and cardiac arrhythmias was not observed. There were no significant differences between ventricular ectopic activity in patients who had been taking antihypertensive medications before randomization and those who had not.

Multivariate analysis considering age, sex, smoking, alcohol consumption, diabetes mellitus, congestive heart failure, coronary artery disease and baseline systolic BP identified age and male gender as significant determinants of the number of ventricular premature contractions in the SHEP cohort. Repetitive forms (ventricular premature contraction pairs and nonsustained ventricular tachycardia) were independently related to age, male gender and baseline systolic BP. When gender was removed from the model, age and coronary artery disease were related to total ventricular premature contractions, and age, coronary artery disease and baseline systolic BP were related to the presence of repetitive forms. In the control group, multivariate analysis using the same independent variables did not identify any significant relation other than age to ventricular premature contractions.

Patients with isolated systolic hypertension have a higher prevalence and frequency of ventricular ectopic activity than normotensive age- and sex-matched control subjects. Also, among patients with isolated systolic hypertension, increasing age and the presence of coronary artery disease were associated with ventricular ectopic activity, whereas serum potassium was not. In our study, a significant proportion (44.7%) of normotensive control subjects (mean age 70 years) had left ventricular hypertrophy by the criteria derived by Levy et al[13] using a cohort with mean age of 42 years for men and 43 years for women. This could be due to the older age of our patients.

TABLE I Comparison of Patients with Isolated Systolic Hypertension to Normotensive Control Subjects and to SHEP Total Cohort

	AECG, SHEP	AECG, Controls	Total SHEP
No. of patients	238	100	4,736
Men/women	107 (45%)/ 131 (55%)	46 (46%)/ 54 (54%)	2,046 (43%)/ 2,690 (57%)
Age (years ± SD)	72 ± 6	70 ± 7*	71.6 ± 6.7
Age range (years)	60–95	60–87	60–>80
Height (inches)	64 ± 4	65 ± 4	64 ± 4
Weight (lb)	169 ± 34	158 ± 28†	162 ± 34
Body mass index (kg/m^2)	29 ± 5	27 ± 4‡	28 ± 5
Systolic BP (mm Hg)	170 ± 9	124 ± 12‡	170 ± 9
Diastolic BP (mm Hg)	78 ± 7	69 ± 8‡	77 ± 10
Serum potassium	4.4 ± 0.5	4.3 ± 0.4	
History of CAD§	34 (15%)	11 (11%)	182 (4%)
Diabetes mellitus	25 (11%)	6 (6%)	478 (10%)
Cigarette smoking	23 (10%)	9 (9%)	602 (12.7%)

*p <0.05 versus AECG, SHEP; † p <0.01 versus AECG, SHEP; ‡ p <0.001 versus AECG, SHEP.

§Evidence of myocardial infarction on the 12-lead electrocardiogram, history of coronary artery bypass surgery or presence of angina.

AECG = ambulatory electrocardiogram; BP = blood pressure; CAD = coronary artery disease; SHEP = Systolic Hypertension in the Elderly Program.

TABLE II Ventricular Ectopic Activity and Left Ventricular Mass in Patients with Isolated Systolic Hypertension and in Normotensive Control Subjects

	SHEP (n = 226)	Control (n = 98)	p Value
Ventricular Ectopic Activity			
VPCs/24 hours	412 ± 1,612	179 ± 479	0.048
VPC pairs/24 hours	2.6 ± 14.8	1.8 ± 9.7	NS
No. (%) with VPCs	190 (84%)	76 (78%)	NS
No. (%) with >10 VPCs	151 (67%)	51 (52%)	0.009
No. (%) of repetitive forms	52 (23%)	15 (15%)	NS
Left Ventricular Mass			
	(n = 95)	(n = 38)	
Left ventricular mass	262 ± 90	234 ± 81	0.104
Left ventricular mass index (g/m)	162 ± 51	144 ± 47	0.064
No. (%) with left ventricular hypertrophy	(76%)	(45%)	0.001

NS = not significant; SHEP = Systolic Hypertension in the Elderly Program; VPC = ventricular premature contractions.

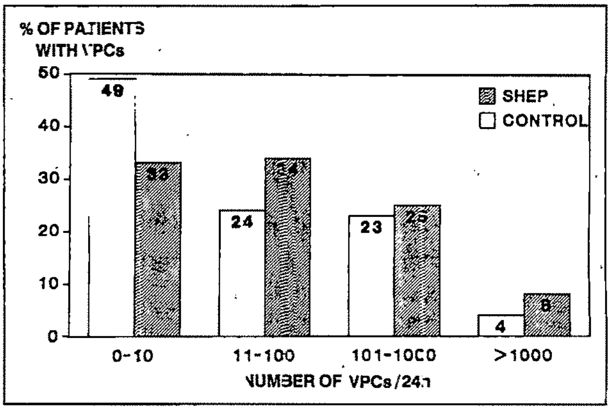

FIGURE 1. Frequency distribution of ventricular premature contractions (VPCs) per 24 hours in patients with isolated systolic hypertension and normotensive control subjects. SHEP = Systolic Hypertension in the Elderly Program.

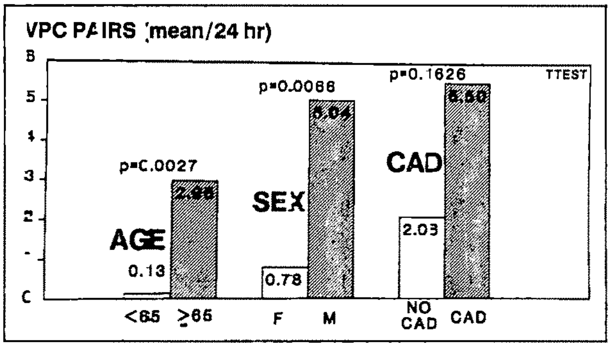

FIGURE 2. Frequency of ventricular premature contraction pairs on 24-hour ambulatory electrocardiography in patients with isolated systolic hypertension by age, sex and history of coronary artery disease (CAD).

In patients with isolated systolic hypertension, increased left ventricular mass index and greater prevalence of left ventricular hypertrophy could be due to the effect of high systolic BP or increased body mass index, or both. A relation of left ventricular mass corrected for height and sex with ventricular ectopic activity was noted, although only 39% of the subjects had acceptable echocardiograms and the calculation of left ventricular mass could have been inaccurate in some patients because of abnormal left ventricular geometry from coronary artery disease.

It is well known that isolated systolic hypertension increases the risk of morbidity and mortality from stroke, coronary artery disease and congestive heart failure.[14-21] Results of the present study indicate that isolated systolic hypertension is also associated with increased ventricular ectopic activity and left ventricular hypertrophy.

Age has been associated with increased ventricular ectopic activity in many patient cohorts including normal subjects and those with coronary artery disease.[22-26] Hypokalemia has been implicated by some investigators as a cause of ventricular ectopic activity, especially in patients taking diuretic drugs.[27-30] In our study, patients had not received antihypertensive medication for ≥4 weeks. The absence of a clear relation between potassium and arrhythmias implies that hypokalemia is not a cause of ventricular ectopy in these elderly patients with systolic hypertension. However, because severe hypokalemia was not observed, the possibility that it may cause arrhythmias in other patients cannot be excluded.

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Detection of Patent Foramen Ovale by Transcranial Contrast Doppler Ultrasound

Ronald Karnik, MD, Claudia Stöllberger, MD, Andreas Valentin, MD, Walther-Benedikt Winkler, MD, and Jörg Slany, MD

The results of recent studies suggest that paradoxical embolism through a right-to-left shunt may more often be the cause of stroke than was previously supposed. Especially in young patients with otherwise unexplained stroke, the prevalence of a patent foramen ovale has been significantly higher (54 and 56%) than in asymptomatic control subjects (10%).[1,2] Currently, contrast echocardiography together with a Valsalva maneuver is the only noninvasive method that reveals this defect.[3,4] Based on the accurracy of transcranial Doppler sonography in the detection of intracerebral emboli during carotid endarterectomy,[5] we investigated whether the route of paradoxical cerebral embolism through patent foramen ovale may be traced reliably by transcranial contrast Doppler sonography.

The study group comprised 36 patients (20 men and 16 women, average age 61 ± 19 years, range 28 to 85) referred to the echocardiography laboratory. Thirty patients were examined for suspected cerebral (n = 27) or peripheral embolism, 4 for suspected left atrial thrombi, and 2 for syncope. Twelve patients had atrial fibrillation, 8 had congestive heart failure, and 3 had coronary heart disease. Eight subjects had valvular heart disease (mitral insufficiency [5], mitral stenosis [2] and aortic stenosis [1]). Informed consent was obtained for transesophageal and contrast studies.

All patients underwent clinical assessment, electrocardiography, and transthoracic and transesophageal echocardiography as part of a routine screening for a cardiac source of emboli. Transesophageal echocardiography was performed using an Aloka SSD 870 with a 5 MHz transesophageal transducer. Contrast transesophageal echocardiography at rest and with a Valsalva maneuver was performed using 10 ml of agitated gelatin (Haemaccel^R, urea-linked gelatin, 35,000 Mw) injected into an antecubital vein. Contrast medium was injected first during the Valsalva maneuver, and care was taken so that the patient began with the release phase as soon as the microbubbles appeared in the right atrium. The injections were repeated twice during spontaneous breathing, followed by a second injection during the Valsalva maneuver. The study was considered positive if ≥1 bubble appeared in the left atrium within 3 cycles after its arrival in the right atrium.

The transcranial Doppler study was performed using a 3-dimensional Doppler scanner (Trans-scan, EME, Ueberlingen, Germany) within 1 hour after transesophageal echocardiography. The 2 MHz pulsed Doppler

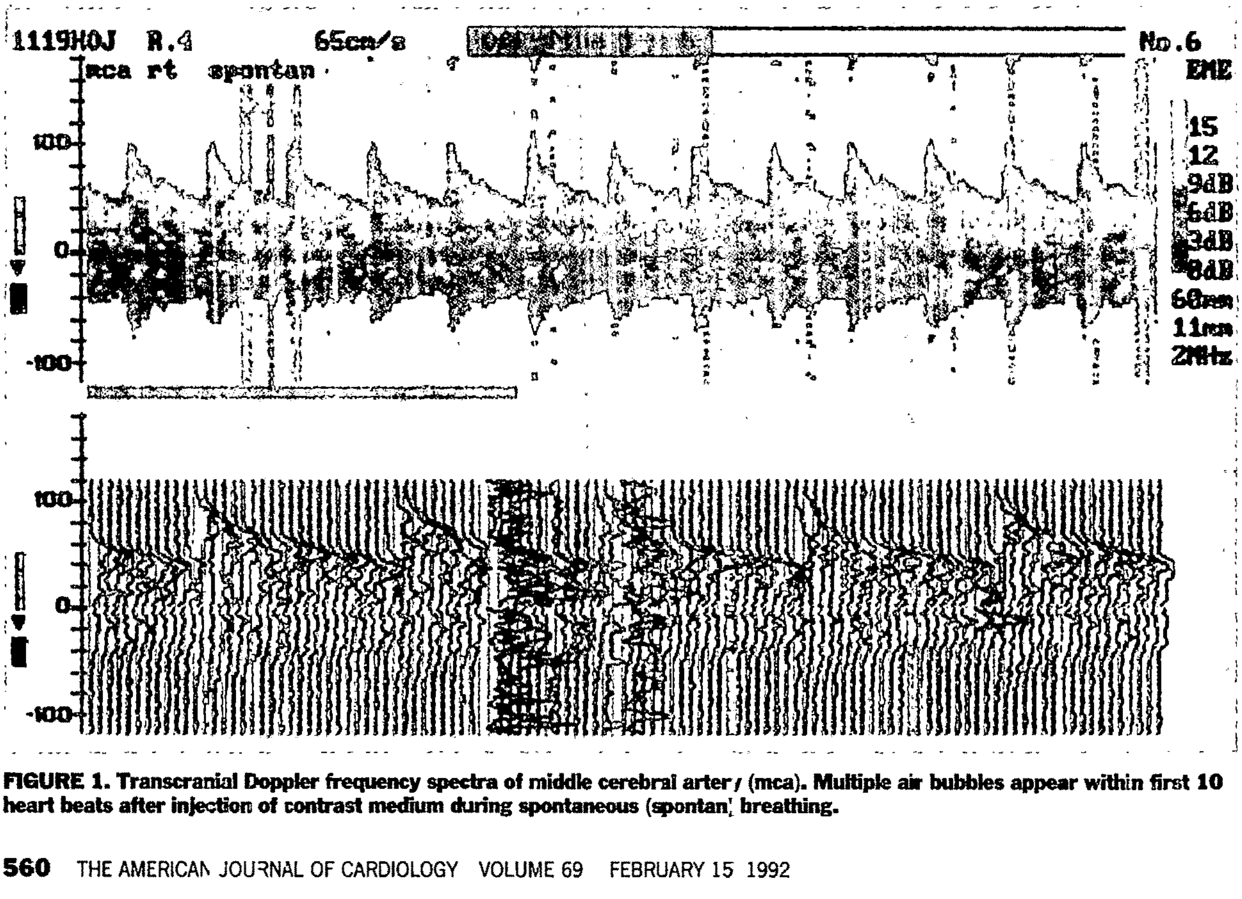

FIGURE 1. Transcranial Doppler frequency spectra of middle cerebral artery (mca). Multiple air bubbles appear within first 10 heart beats after injection of contrast medium during spontaneous (spontan) breathing.

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probe of the Trans-scan was placed against the side of the skull just above the zygomatic arch. The middle cerebral artery on both sides was insonated at a depth of 45 to 60 mm. The optimal signal of 1 side was used for further evaluation that was performed in the same fashion as the echocardiographic studies. Bubble signals were defined as described by Spencer et al[5]*: signals with a very high amplitude (up to 60 dB greater than the background Doppler signal), with harmonic quality and a relatively narrow spectrum. The trancranial Doppler study was defined as positive if ≥5 bubble signals were recorded within the first 10 heart beats after completing the injection of the contrast medium.*

The transcranial examination was assessed independently of the echocardiographic results. All echocardiographic studies were tape-recorded and reviewed by a blinded observer. In all cases, review confirmed the initial diagnosis concerning presence or absence of an intracardiac shunt.

Transesophageal echocardiography was considered as the golden standard. Sensitivity, specificity and predictive values of transcranial Doppler sonography were calculated by standard formulas.

Fifteen patients had evidence of right-to-left shunting at the atrial level shown by contrast transesophageal echocardiography; 5 of these had an atrial septal aneurysm, and 1 had an atrial septal defect. The patent foramen ovale was detected during spontaneous breathing in 9 subjects and with the Valsalva maneuver in the remaining 6.

Examples of frequency spectra of the middle cerebral artery demonstrating the appearance of microbubbles during normal breathing and the Valsalva maneuver are shown in Figures 1 and 2. In 13 patients, bubble signals were identified in the middle cerebral artery during the first 10 heart beats. The right-to-left shunt was established during spontaneous breathing in 8 subjects and with the Valsalva maneuver in 5. In all patients with a positive test during normal breathing, the number of air bubbles detected in the basal cerebral arteries was increased by the Valsalva maneuver. There were 2 patients with false negative findings: in both, no air bubbles appeared during the first 10 heart beats in the middle cerebral artery. In 1 patient, 8 air bubbles were detected during the Valsalva maneuver after 10 to 15 heart beats. In the other patient, 3 to 5 air bubbles were seen between the first 10 to 20 heart beats, both during normal breathing and after provocation.

Transcranial contrast Doppler sonography using transesophageal echocardiography as reference method showed a sensitivity of 87%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 91%.

Contrast echocardiography is a firmly established method in the detection of patent foramen ovale.[3,4] We used the transesophageal approach as reference method, because it has been shown to be far superior to transthoracic studies.[6] However, transesophageal echocardiography is a semiinvasive procedure with low but definite risk. It is not applicable to all patients. It may be especially difficult to perform in patients with acute stroke, the most frequent clinical manifestation of paradoxical embolism. Furthermore, echocardiography, whether performed by the transthoracic or the transesophageal route, needs skilled and experienced personnel who may not be readily available in departments treating stroke patients.

Transcranial Doppler sonography, a simple technique familiar to neurologists, may overcome some of these

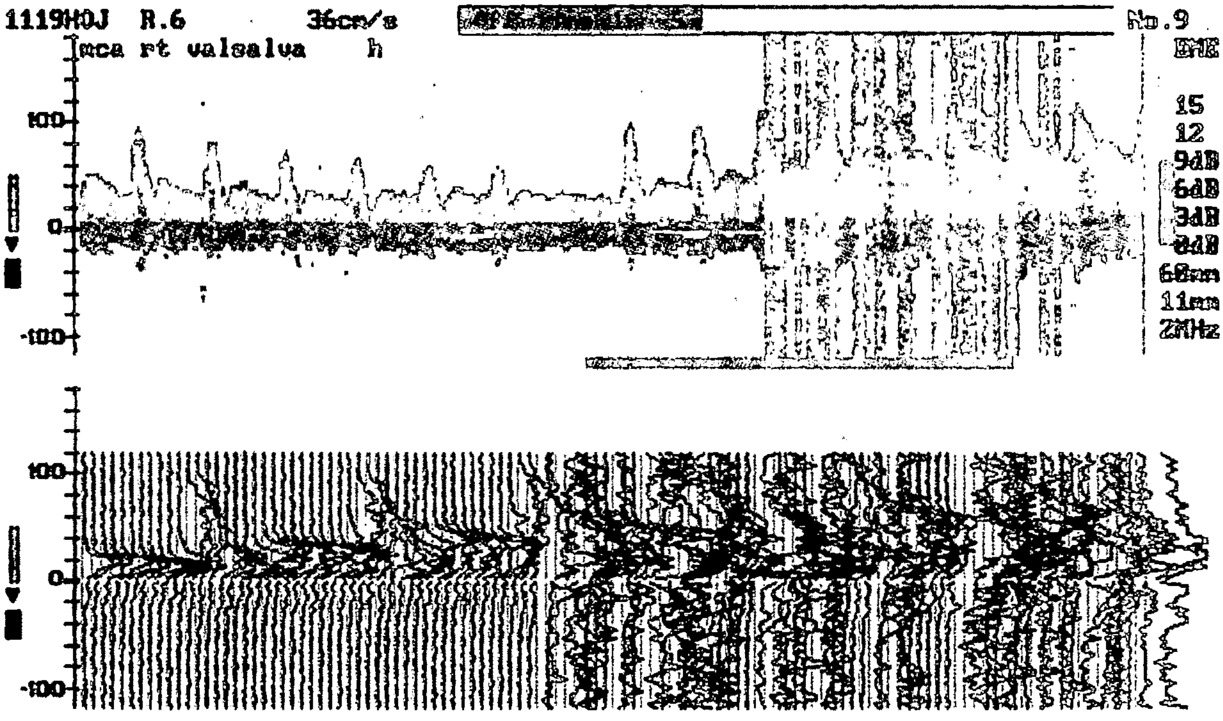

FIGURE 2. Transcranial Doppler frequency spectra of middle cerebral artery (mca). Shower of micro air bubbles passes through vessel, 2 heart beats after release of Valsalva maneuver.

limitations if it is proved to be sufficiently sensitive and specific for the assessment of shunted contrast medium. In the majority of patients, the flow in the proximal portion of the middle cerebral artery can be visualized readily. Spencer et al[5] showed that microemboli dislodged during carotid endarterectomy are detected reliably by this method. We used their criteria for microemboli to define microbubbles.

In a pilot study of 5 patients with patent foramen ovale detected by contrast transesophageal echocardiography, normal saline solution as contrast medium yielded questionable results in the middle cerebral artery, whereas an agitated 3.5% gelatin solution produced strong, reproducible echo signals. Gelatin solution is a widely used colloid for volume substitution and hemodilution. No adverse reactions were experienced by any patient in this series.

In accordance with the normal transit times, micro air bubbles appeared in the middle cerebral artery within 10 heart beats after injection. Single bubble signals occurring later were thought to be due to either intrapulmonary shunting or normal pulmonary passage. Late bubbles are often found in contrast echocardiograms and are not indicative of intracardiac shunts.

Possible reasons for false negative results in 2 of the 15 patients include: injection of insufficiently agitated contrast medium, an extremely peripheral injection site and prolonged transit times due to cardiac insufficiency.

By using strict criteria, transcranial contrast sonography proved to be an excellent method in revealing intracardiac shunts. Its use may have clinical value in patients presenting with a nonhemorrhagic stroke or peripheral embolism without heart disease. Particularly in stroke patients, it may be used complementarily to noninvasive examination of the cerebral vessels by Duplex sonography and transcranial ultrasound. A positive contrast finding neither localizes the site of the shunt in the heart nor demonstrates pradoxical embolism. However, any right-to-left shunt in the heart and even in the lung may serve as a pathway for paradoxical embolism. In such cases, venous thrombosis should be searched for immediately, because it is the second prerequisite for paradoxical embolism. A positive phlebogram is strong evidence for paradoxical embolism in this setting.

Although definite treatment for this syndrome is yet unknown, full heparinization appears warranted to prevent further thromboembolic complications. A negative contrast finding on transcranial Doppler sonography should prompt echocardiographic studies to search for other cardiac sources of embolism.

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Estimation of Pulmonary Arterial Wedge Pressure by Pulsed Doppler Echocardiography and Phonocardiography

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Pulsed Doppler echocardiography is widely used to evaluate left ventricular diastolic function. Limited data are available regarding the use of this technique in the noninvasive assessment of left ventricular filling pressure. Recent Doppler studies indicated a direct relation between the ratio of early-to-late transmitral diastolic filling velocity (E/A ratio) and left ventricular filling pressure.[1–4] In addition, earlier work showed that left ventricular isovolumic relaxation time is inversely related to pulmonary capillary wedge pressure.[5] The aims of this study were to further examine these relations, and to determine if E/A ratio and isovolumic relaxation time could be used to predict pulmonary arterial wedge pressure noninvasively.

Transmitral Doppler flow velocities, phonocardiograms and pulmonary arterial wedge pressures were recorded simultaneously in 35 patients aged 50 to 94 years (mean 72 ± 10) undergoing bedside hemodynamic monitoring with a Swan-Ganz catheter. All patients were in sinus rhythm (mean heart rate 85 ± 15 beats/min). Patients with unstable angina, mitral stenosis and more than mild mitral or aortic regurgitation were excluded. To minimize the influence of age on transmitral flow velocity, patients aged <50 years were also excluded. The diagnoses were ischemic heart disease in 16 patients, hypertensive heart disease in 5, dilated cardiomyopathy in 4, aortic stenosis in 3, restrictive cardiomyopathy in 1, and hypertrophic cardiomyopathy in 1. Five patients without apparent heart disease underwent pulmonary artery catheterization for assessment of fluid status. Pulsed Doppler studies were obtained from the apical 4-chamber view with the sample volume in the left ventricle at the tips of the mitral leaflets. Seven to 10 consecutive beats were averaged, and recordings were obtained at a

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paper speed of 100 mm/s. Peak mitral flow velocity in early (E) and late (A) diastole, and E/A ratio were measured as shown in Figure 1. Left ventricular isovolumic relaxation time was measured from aortic closure on the phonocardiogram to the onset of mitral flow (Figure 1). Measurements were obtained without knowledge of the catheterization findings. Pulmonary arterial wedge pressure was measured at end-expiration with the patient supine and the reference level for zero pressure at midchest. Data are expressed as mean ± SD. The relations between Doppler variables and invasively measured pulmonary arterial wedge pressure were compared using linear regression.

Invasively measured pulmonary arterial wedge pressure ranged from 2 to 40 mm Hg (mean 16 ± 9). E/A ratio measured by pulsed Doppler echocardiography ranged from 0.64 to 2.74 and showed a strong positive correlation with pulmonary arterial wedge pressure (r = 0.83) (Figure 2A). Isovolumic relaxation time ranged from 41 to 127 ms and correlated inversely with pulmonary arterial wedge pressure (r = −0.54) (Figure 2B). The best correlation with wedge pressure was obtained when these 2 variables were combined and expressed as E/A ratio/isovolumic relaxation time. This ratio ranged from 0.006 to 0.051 and showed an excellent correlation with pulmonary arterial wedge pressure (r = 0.93, standard error of the estimate 3 mm Hg). The relation between these variables is expressed by the regression equation: pulmonary arterial wedge pressure = [805(E/A ratio)/isovolumic relaxation time] + 1.3.

This study was undertaken to determine if 2 easily measured indexes (E/A ratio and isovolumic relaxation time) could provide a reliable noninvasive estimate of left ventricular filling pressure. We found that pulmonary arterial wedge pressure correlated directly with E/A ratio (r = 0.83) and inversely with isovolumic relaxation time (r = −0.54). By combining these values and expressing them as E/A ratio/isovolumic relaxation time there was further improvement in the correlation coefficient (r = 0.93). Our data are consistent with recent clinical and experimental studies indicating that E/A ratio and isovolumic relaxation time frequently respond in a predictable manner to changes in left ventricular filling pressure.[1-4,6,7] Channer et al[1] used this ratio to estimate left ventricular filling pressure noninvasively in patients with coronary artery disease. They found a significant

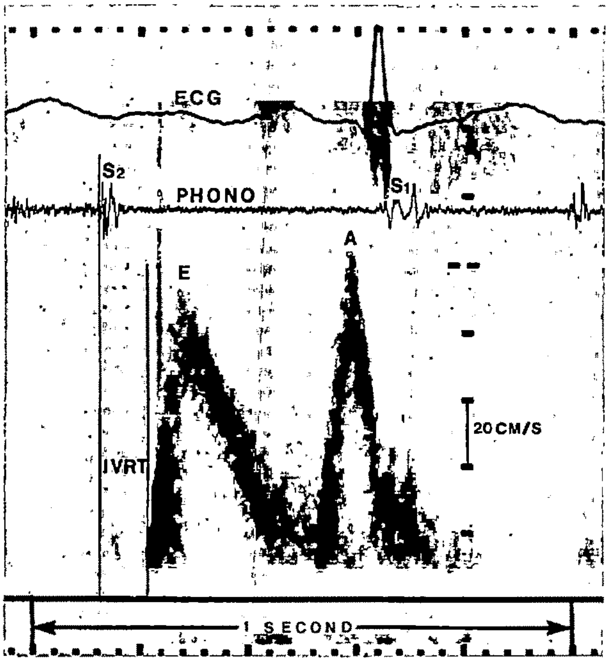

FIGURE 1. Phonocardiogram (PHONO) and pulsed Doppler recording of mitral inflow velocity showing peak early (E) and late (A) diastolic velocities. Isovolumic relaxation time (IVRT) is measured from aortic valve closure on phonocardiogram (S₂) to onset of mitral flow. ECG = electrocardiogram.

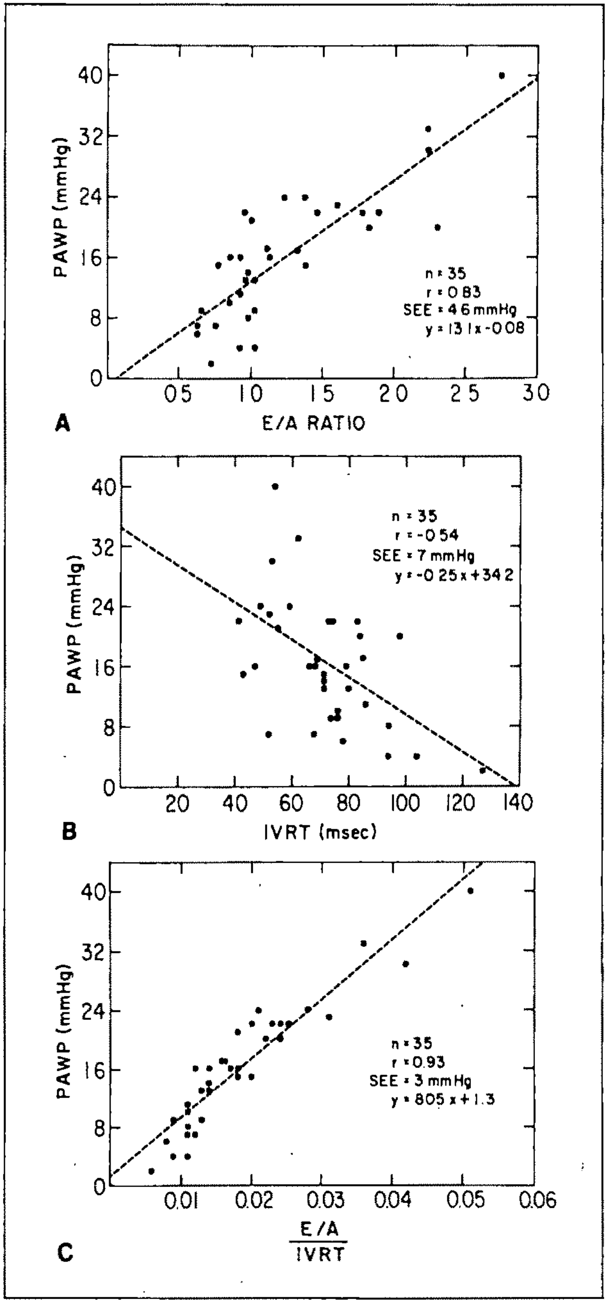

FIGURE 2. *A*, relation between early-to-late transmitral diastolic filling velocity (E/A) ratio recorded by Doppler echocardiography and pulmonary arterial wedge pressure (PAWP). *B*, relation between isovolumic relaxation time (IVRT) and PAWP. *C*, E/A ratio/IVRT compared with PAWP.

linear correlation between E/A ratio and left ventricular end-diastolic pressure. Comparable findings have also been observed in dilated cardiomyopathy, restrictive heart disease, aortic stenosis and recent myocardial infarction.[2-4,6,8]

Use of isovolumic relaxation time to estimate pulmonary arterial wedge pressure noninvasively was first reported in patients with mitral stenosis. Using phonocardiography, it was shown that isovolumic relaxation time is inversely related to pulmonary arterial wedge pressure.[9] Subsequent echocardiographic studies extended these observations to patients with many other types of heart disease.[5] Recently, Appleton et al[2] measured isovolumic relaxation time by recording the interval from aortic closure on the phonocardiogram to the onset of mitral flow on the Doppler velocity tracing. Again, a significant negative correlation ($r = -0.62$) was found between isovolumic relaxation time and pulmonary arterial wedge pressure.

The excellent correlation between E/A ratio/isovolumic relaxation time and pulmonary arterial wedge pressure in the present study may be related to our exclusion of patients with acute myocardial ischemia, significant mitral or aortic regurgitation and mitral stenosis. These conditions can alter transmitral diastolic flow patterns independently of changes in filling pressure. The reduction in E/A ratio that accompanies aging must also be considered.[10] This ratio differs significantly in younger and older normal subjects. To minimize this factor, only patients aged >50 years were included. Thus, our data are only applicable to an older population. Heart rate can also affect diastolic filling. The E/A ratio will decrease as heart rate increases. However, because isovolumic relaxation time is shortened concomitantly, the net effect will be minimal.

Diastolic filling is a complex sequence of interrelated events and is influenced by many factors. Consequently, E/A ratio/isovolumic relaxation time cannot always achieve the accuracy of invasively derived pulmonary arterial wedge pressure. However, in selected patients it can provide useful hemodynamic information and may avoid the need for an invasive procedure.

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Richard Lower (1631–1691): A Pioneer of Cardiologic Research

Andrew J. Larner, BM, MRCP

The year 1991 marks the 300th anniversary of the death of Richard Lower, a 17th century English anatomist and physiologist who undertook pioneering studies of the heart and circulation.[1] His *Tractatus de Corde*, which summarizes much of his work, was published in 1669 and, though little known, is a landmark in the history of cardiology.

A Cornishman by birth, Lower studied at Oxford and became noted for his practical skills in dissection and vivisection. His anatomic studies of the nervous system with Thomas Willis in the early 1660s resulted in the description of the spinal accessory nerve and in the naming of the Circle of Willis.

Turning his attention to the circulation, Lower's dexterity produced a new understanding of the structure of the heart, particularly the cardiac musculature. Observations of the layered helical disposition of muscle fibers in boiled hearts led Lower to believe that muscle contraction forced the ventricular walls together, thus squeezing out the contained blood; this was at a time when "fermentation" or "ebullition" of the blood in the heart was generally thought to produce its motion, heat and color change. Lower also described the innervation of the heart and gave a clear account of the experimental effects of division of the vagus nerve. In his description of the internal structure of the heart, Lower identified the intervenous tubercle in the right atrium, which now bears his eponymous stamp.

Experiments performed at the Royal Society in London in 1667 in collaboration with the physicist Robert Hooke brought new insights into the nature of respiration. The difference in the color of arterial and venous blood had long perplexed physiologists; Lower was able to demonstrate that this color change unequivocally occurred during the pulmonary transit of the blood, and not in the left ventricle, as previously thought. By connecting 2 pairs of bellows in series, a dog's lungs could be insufflated with a constant stream of air independent of thoracic movements; blood in the pulmonary vein was florid red in color, whereas after asphyxiation it remained a deep purple. It was thus demonstrated that air, or a component of it, coming into contact with blood in the lungs produced the color change and was essential to life. These experiments prompted Lower's election to the Fellowship of the Royal Society in October 1667.

Lower also experimented with the newly discovered techniques for infusing substances into the circulation by way of intravenous quills or metal syringes. He devised a way to convey blood by means of pipes from the circulation of 1 dog to another, and subsequently applied the technique to man, so performing the first successful human transfusion in England in November 1667. This whole episode is recorded by Samuel Pepys in his diary.

Aside from his written works, Lower's only memorial is to have the male ward of the Nuffield Department of Clinical Medicine at the John Radcliffe Hospital in Oxford named for him. The importance of his fundamental contributions to the understanding of cardiac structure and function, and circulatory physiology deserves wider recognition.

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Assessment by Echocardiogram of Left Ventricular Diastolic Function in Healthy Subjects Using the Atrioventricular Plane Displacement

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Recent echocardiographic studies have shown that the atrioventricular (AV) valve plane displacement toward the apex in systole plays an important role in the pump function of the left ventricle.[1–6] The method of recording the AV plane displacement is simple and the magnitude of the AV plane displacement can be used to assess left ventricular systolic function in patients with acute myocardial infarction, coronary artery disease and severe chronic congestive heart failure.[5–7] At the start of diastole, the AV plane begins to ascend rapidly toward the atrium away from the apex. Atrial systole also contributes to ventricular filling by further displacing the AV plane in the same direction, and this is noticed in the last part of the diastolic phase of AV plane displacement and is associated with the P wave of the electrocardiogram.[8] The purpose of this study was to evaluate the diastolic function in healthy control subjects of different age groups by relating the motion of the AV plane due to atrial systole to the total diastolic ascent of the AV plane.

One hundred persons (medical students, physicians and other hospital personnel), 78 men and 22 women aged <75 years, were included in the study. None had a history of cardiac or pulmonary disease or hypertension and all the subjects showed normal findings as revealed by physical examination, resting electrocardiography and echocardiography. The subjects were divided into 3

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different age groups: group I, <35 years; group II, 35 to 54 years; and group III, 55 to 74 years.

Echocardiography was performed with the subjects in the left lateral decubitus position using an Aloka SSD-870 and a 2.5 MHz transducer. The method of recording the total displacement of the AV plane in the left ventricle has been described elsewhere.[2,5,6] *In brief, on the real-time 2-dimensional apical 4-chamber view the M-mode cursor was placed at the septal border of the left ventricular AV plane (mitral ring) in such a way so that the AV plane moved along the M-mode line and the displacement was recorded in M-mode. By moving the M-mode cursor to the lateral border of the AV plane, the displacement of the lateral wall was also recorded. Similarly, the AV plane displacement at the anterior and posterior walls was recorded from the apical 2-chamber view. The total displacement of the AV plane was measured using the leading edge of the echoes (Figure 1). The magnitude of the AV plane displacement was expressed as the mean of 5 consecutive cardiac cycles.*

The motion caused by atrial contraction was recorded from the diastolic phase when the AV plane moves away from the transducer and apex toward the atrial roof (Figure 1). The last part of the diastolic AV plane displacement, which is associated with the P wave of the electrocardiogram, is due to atrial systole.[8] *The contribution of atrial systole to left ventricular filling was calculated from the ratio of the magnitude of motion due to atrial systole to the total diastolic AV plane displacement. Both the total displacement and motion due to atrial systole was recorded at all left ventricular walls. The magnitude of displacements was similar, and therefore only at one site was reported. In addition, pulsed-wave Doppler was recorded over the mitral valve for early (E) and late (A) velocity profiles of the transmitral flow. The right ventricular AV plane displacement at the free wall and atrial systolic component were recorded in a way similar to that for the left ventricle from the apical 4-chamber view (Figure 2).*

Results are given in mean ± SD. Comparisons of the results were obtained using Student's t *test. Linear regression analysis has been used to test the relation between 2 different parameters. Nineteen subjects were studied 4 times by 2 different investigators each time at 2 different occasions to test the reproducibility for the AV plane displacement at the right ventricular free wall and 1 site on the left ventricle (lateral wall). Both the investigators were well trained in echocardiography. One of them (investigator I) was well accustomed to recording the AV plane displacement, and the other (investigator*

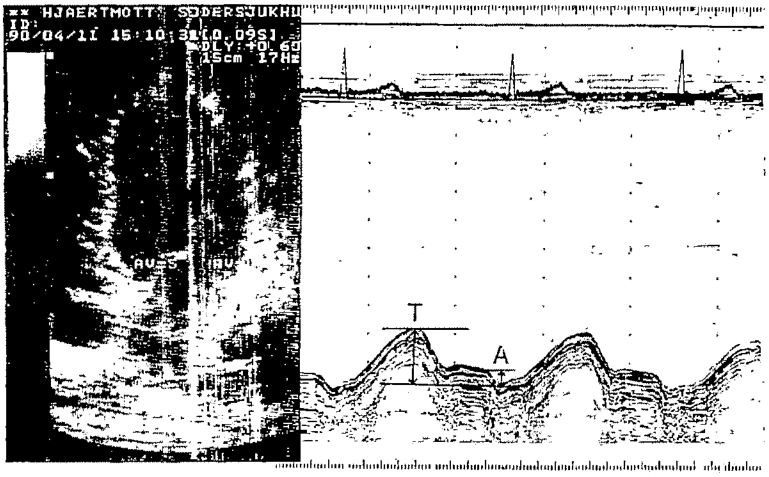

FIGURE 1. Apical 4-chamber view *(left)* in a healthy subject with the M-mode cursor placed at the septal wall of the atrioventricular (AV) plane. The magnitude of the total AV plane displacement (T) and motion due to atrial systole (A) is shown in M-mode *(right)*.

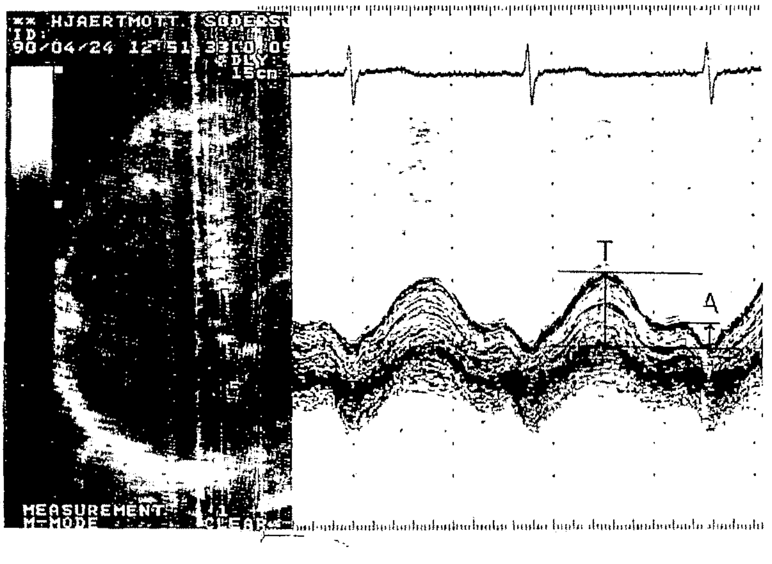

FIGURE 2. Apical 4-chamber view *(left)* in a healthy subject with the M-mode cursor placed at the atrioventricular (AV) plane of the right ventricular free wall. On M-mode echocardiography *(right)*, the total AV plane displacement (T) and atrial displacement (A) is shown.

TABLE I Basic Clinical and Echocardiographic Parameters

Variables	All Subjects (n = 100)	Group I (n = 32)	Group II (n = 34)	Group III (n = 34)
Age (years)	45 ± 15	28 ± 4	44 ± 7	62 ± 5
Heart rate (beats/min)	65 ± 13	66 ± 13	64 ± 8	64 ± 9
Systolic blood pressure (mm Hg)	126 ± 12	120 ± 10	126 ± 9	131 ± 10
Diastolic blood pressure (mm Hg)	80 ± 7	78 ± 5	81 ± 7	82 ± 6
Left ventricular end-diastolic dimension (mm)	51 ± 4	50 ± 3	51 ± 4	53 ± 3
Left atrium (mm)	35 ± 5	33 ± 3	34 ± 5	37 ± 3
Fractional shortening (%)	38 ± 5	38 ± 4	38 ± 4	37 ± 5

TABLE II Different Parameters for Diastolic Atrioventricular (AV) Plane Displacement of the Left Ventricle

Variables	All Subjects (n = 100)	Group I (n = 32)	Group II (n = 34)	Group III (n = 34)
Total AV plane displacement (mm)	15.5 ± 2.0	17 ± 4.0	15 ± 2.0	14.5 ± 2.0
Motion due to left atrial systole (mm)	5.0 ± 1.5	4.0 ± 1.0	5.0 ± 1.5	6.0 ± 1.0
Atrial contribution to total AV plane displacement (%)	32 ± 10	23 ± 5.0	33 ± 8.0	41 ± 8.0

II) had little experience with it. After recording the AV plane displacement, measurements were performed independently for interobserver and intraobserver variability using analysis of variance.

The basic clinical and echocardiographic parameters for the total population and for individual groups of subjects are listed in Table I. The AV plane displacement at the left ventricle in different groups is listed in Table II. The total displacement was significantly greater in group I than in groups II (p <0.01) and III (p <0.001). The atrial contribution to the total diastolic AV plane displacement was significantly increased in groups II and III compared with group I (p <0.001 for both) and also in group III compared with group II (p <0.001). With the exception of 1 subject in group II and 2 in group III, all subjects in the 3 groups had atrial contributions to the total AV plane displacement of ≤50%. There was a good correlation between the atrial contributions to diastolic AV plane displacement and the age of the subjects (Figure 3). Doppler recordings were available for 55 of the subjects. The Doppler recorded A- and E-wave velocities were 0.5 ± 0.15 and 0.8 ± 0.13 m/s, respectively. The A/E was 65% ± 17. The correlation between the atrial contribution to diastolic AV plane displacement and the transmitral A/E waves was good (Figure 4).

The AV plane displacement at the right ventricle was available for 19 of the subjects and it was significantly increased (25 ± 3 mm, p <0.001) compared with the left ventricular AV plane displacement. The motion due to right atrial systole in the diastolic phase of the AV plane displacement was also higher (7 ± 1.5 mm, p <0.001) than the left atrial AV plane displacement. However, the right atrial contribution to total displacement of the right ventricular valve plane (28%) was similar to that of the left side.

The intra- and interobserver variabilities for the 4 different investigations by 2 different investigators were low (<1 mm for both total AV plane displacement and motion due to atrial contraction). When a separate intraobserver variability test was performed for 2 different investigators, similar low figures were also obtained (investigator I, ≤0.81 mm; investigator II, ≤1.1 mm for the above-mentioned results).

The systolic descent of the AV plane toward the relatively stable apex has been shown to be a very useful echocardiographic index of left ventricular systolic function.[1,3,4,6,7] Displacement of the AV plane toward the apex is due to the longitudinal shortening of the muscle fibers of the left ventricle. During diastole, the AV plane rapidly ascends away from the apex toward the atrium. The filling of the left ventricle is determined by ventricular relaxation and atrial systole. The last part of the diastolic AV plane displacement, which is associated with the P wave of the electrocardiogram[8] and the "A" wave of the transmitral Doppler flow, is due to atrial systole.

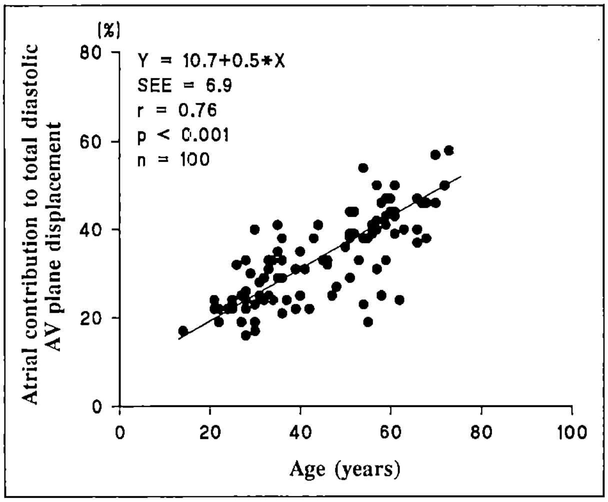

FIGURE 3. Correlation between age and atrial contribution to diastolic atrioventricular (AV) plane displacement.

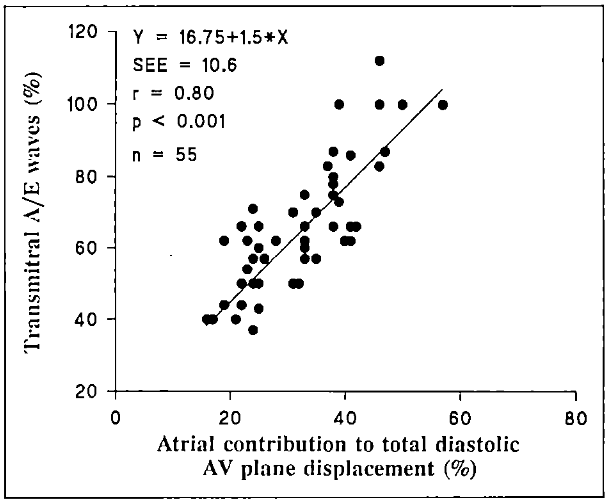

FIGURE 4. Correlation between atrial contribution to diastolic atrioventricular (AV) plane displacement and ratio of transmitral late (A) and early (E) velocity waves.

The ratio of the motion due to atrial systole to the total diastolic AV plane displacement can therefore be considered to represent the contribution of atrial systole to left ventricular filling. In our study, all but 3 control subjects had an atrial contribution of ≤50%. According to Starling's law of the heart,[9] the ventricular contraction is dependent on the end-diastolic fiber length and pressure. The atrium, by virtue of its active contraction, can modify ventricular end-diastolic pressure and end-diastolic fiber length, and thereby is capable of modifying the performance of the ventricle. In this study, younger subjects showed a relatively mild atrial systole, compared with older groups, as judged from the decreased ratio between atrial AV and total AV plane displacement. These findings reflect the phenomenon of decreased left ventricular compliance with advancing age with a concomitant compensatory augmentation of active atrial emptying as reflected by an increase in atrial AV plane displacement in older age groups. This was further supported by the finding of a good linear correlation of age with the atrial contribution to AV plane displacement. Using different techniques, others have also demonstrated a decrease in diastolic function with advanced age.[10,11] The ratio of the height of the "A" wave to the "E" wave in the Doppler velocity curve across the mitral valve is frequently used to express the contribution of atrial systole to left ventricular filling. With increasing age, this ratio also increases because of a larger contribution of atrial systole to overall left ventricular filling.[10] In this study there was a good linear correlation between A/E waves and the contribution of atrial AV plane displacement, which further supports the usefulness of the new echocardiographic parameter for the assessment of diastolic function.

Right ventricular systolic descent of the AV plane is related to systolic function in a way similar to that of the left ventricle. However, the displacement was significantly greater than left ventricular AV plane displacement. This is in agreement with Rushmer et al[12] and reflects the predominance of longitudinal shortening of the right ventricular free wall with little shortening of its width. This is probably due to different patterns of muscle structure in the right ventricle. Although the right atrial AV plane displacement was significantly increased compared with the left atrial AV plane displacement, the percentage of atrial contribution to right ventricular filling was quite similar to that of the left ventricle. However, in calculating AV plane displacement of the right ventricular free wall, we probably underestimated the absolute excursion because of a slightly arc-like movement of the recording site, causing a narrow angle with the ultrasound beam.

In conclusion, this study provides a simple echocardiographic means of assessing left ventricular diastolic function in a series of healthy subjects. The method is highly reproducible with low inter- and intraobserver variabilities. Normal values of atrial AV plane displacement in relation to total AV plane displacement for different age groups of healthy subjects provide further information regarding the age-related changes in diastolic function. Further studies, however, are needed to assess its significance, especially in patients with pathologic impairment in diastolic function.

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Cytologic Analysis of Pericardial Effusion Complicating Extracardiac Malignancy

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Pericardial or myocardial involvement, or both, in patients with extracardiac malignancy is uncommon.[1–2] Recently, increased awareness of pericardial complications in patients with malignancy, and the introduction of noninvasive diagnostic techniques such as echocardiography[2–3] and computed tomographic scanning[4] have improved the diagnosis of pericardial effusion. Pericardial effusion in patients with extracardiac neoplasm does not necessarily denote metastases. The establishment of the malignant nature of pericardial effusion is based on either histologic documentation of malignant pericardial involvement or cytologic demonstration of malignant cells in the pericardial fluid. Only a few cytologic studies of pericardial fluid were reported in the literature,[5–12] and only 1 was based on a large series.[8] We report our experience with cytology of pericardial fluid in

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TABLE I Clinical and Laboratory Features of Patients Correlated with the Cytologic Findings of Pericardial Effusion

Features	Malignant Definite	Malignant Suspected	Benign
Number of patients	34	8	18
Female	17	4	16
Male	17	4	2
Age (yrs)			
Median	56	63	54
Range	13–70	19–79	19–75
Time interval (mos) between the diagnosis of primary neoplasm and pericardial effusion			
Median	9	9	36
Range	0–219	0–73	0–204
Number of patients with cardiac tamponade	23	0	8
As a primary manifestation	5	0	0
Volume (ml) of pericardial fluid removed			
Median	630	1210	470
Range	80–2,250	210–2,750	70–1,750
Quality of pericardial fluid (no. of pts.)			
Purulent	0	0	2
Serous	3	0	4
Hemorrhagic	30	8	10
Not specified	1	0	3

TABLE II Histology of Primary Malignancy Correlated with Cytologic Findings of Pericardial Effusion

Histologic Type of Primary Malignancy	Malignant Definite	Malignant Suspected	Benign
Adenocarcinoma	24	5	8
Undifferentiated carcinoma	0	1	1
Squamous cell carcinoma	2	1	2
Small cell carcinoma	2	0	3
Large cell carcinoma	1	0	0
Mixed germ cell tumor	0	1	0
Malignant melanoma	0	0	2
Lymphoma non-Hodgkin	3	0	0
Hodgkin	0	0	1
Lymphocytic leukemia	2	0	0
Multiple myeloma	0	0	1
Total	34	8	18

TABLE III Cytologic Findings of Pericardial Fluid

Cytologic Findings	Number of Patients
Satisfactory material	60
Nonmalignant cells	11
Atypical cells	7
Suspected malignant cells	8
Malignant cells	34
Adenocarcinoma	16
Small cell carcinoma	3
Lymphoma	3
Leukemia	1
Squamous cell carcinoma	1
Not otherwise specified	10
Unsatisfactory material	2
Total	62

62 consecutive patients with extracardiac malignancy and symptomatic pericardial effusion.

From January 1977 to December 1989, pericardial fluids from 62 patients with histologically confirmed extracardiac neoplasm, who were treated for symptomatic pericardial effusion, were examined at the Department of Diagnostic Cytology, Rambam Medical Center. The diagnosis and amount of pericardial effusion were determined by echocardiography. For the purpose of cytologic evaluation, pericardial fluid specimens were mixed with equal amounts of 50% ethyl alcohol, centrifuged, and the sediment was spread on a prealbuminized glass slide. The smears were fixed instantaneously in 95% ethyl alcohol for 60 minutes, and then stained by the Papanicolaou method. The cytologic findings were reported as follows: acellular, unsatisfactory, nonmalignant, atypical-reactive, suspected malignancy and malignant. Follow-up information on each patient was recorded. We considered nonmalignant and atypical-reactive aspirates as benign cytologic diagnoses, whereas suspected and definite malignancy were regarded as malignant.

The pericardial fluid specimens were satisfactory for cytologic analysis in 60 of the 62 (98%) patients constituting the study group (Table I). The sites of the primary tumors were lung in 22 patients (38%), breast in 19 (33%), miscellaneous in 12 (21%), and unknown in 5 (9%). Table II depicts the histology of primary malignancy. At the time of cytologic examination, >73% of the patients had either cytologic evidence of metastases or imaging findings suggestive of metastases. Radiation to the heart region >4,000 rad before the development of pericardial effusion was given to 7 patients. Two-dimensional echocardiographic evidence of large pericardial effusion (>500 ml) was demonstrated in 48 patients. Pericardiocentesis afforded prompt symptomatic relief of pericardial effusion in all patients. For some patients, this relief was only temporary. Histologic preparations were analyzed from pericardial tissue obtained by pericardiectomy (to control cardiac tamponade) in 7 patients and by autopsy in 5. Smears and cultures for bacterial infection (including tuberculosis) were negative in all except 2 patients with purulent pericardial effusion due to Staphylococcus. The cytologic findings of pericardial effusion are listed in Table III. Of the 9 patients with histologic evidence of malignant pericardial disease, pericardial fluid cytology revealed malignant cells in 5 (56%), and suspected malignancy in 2 (22%), but did not demonstrate malignancy in 2 (22%). Of the 3 patients with benign pericardial histology, the cytologic findings revealed malignant cells in 1, suspected malignancy in another, and nonmalignant cells in the third. Pericardial effusion was considered malignant cytologically or histologically in 38 patients (63%) and was suspected for malignancy only by cytology in 6 (10%). In 16 patients (27%), neither cytology nor histology revealed malignancy. Using pericardial histology as a gold standard, the sensitivity of the cytologic findings (definite and suspected malignancy) was 78% (7 of 9 patients). The time interval between pericardiocentesis and death for the 38 patients with positive cytology or histol-

TABLE IV Results of Previously Reported Series on the Frequency of Malignant Cells Obtained by Cytology of Pericardial Effusion in Patients with Extracardiac Malignancy

Investigators	Frequency of Malignant Cells (%)
Zipf and Johnston[5]	13/15 (87)
Reyes et al[7]	6/9 (67)
Yazdi et al[8]	41/72 (57)
Fraser et al[9]	17/26 (81)
Posner et al[10]	11/13 (85)
Lopez et al[11]	11/12 (92)
Tatsuta et al[12]	6/7 (86)
Tatsuta et al[12]*	7/7 (100)
Pinto[13]*	2/2 (100)
Present series	42/62 (68)

*Denotes the cytologic findings while using a combination of cytologic examination and carcinoembryonic antigen.

ogy and for the 5 with suspected positive cytology was 0 to 48 months (median 2), whereas that for the 17 with negative cytology or histology was 1 to 140 months (median 9).

Lung and breast cancer were the 2 most frequent primary tumors associated with symptomatic pericardial effusion. This finding is explained by the frequent occurrence of these malignancies and by the proximity of these neoplasms to the pericardium. Similar findings were reported by other investigators.[5,7–10] The median time interval between the diagnosis of the extracardiac neoplasm and detection of symptomatic pericardial effusion was 11 months. At that time 73% of the patients had either cytological evidence of metastases or imaging findings suggestive of metastases. These findings suggest that symptomatic malignant and benign pericardial effusion usually occur late in the course of disseminated malignancy. Symptomatic malignant pericardial effusion seldom represents the initial manifestation of extracardiac malignancy[2,4,7–9,10–13]; this occurred in only 5 (16%) of our patients. The etiology of symptomatic pericardial effusion may be malignant or benign,[10] and distinguishing between these etiologies has important therapeutic and prognostic implications. However, as demonstrated in the present study, the various clinical findings were not specific and did not indicate the etiology of the pericardial disease. The malignant nature of pericardial effusion can be established only by microscopic demonstration of malignant cells in pericardial tissue or fluid. Surgical biopsy for the sole purpose of establishing a tissue diagnosis may be detrimental from the standpoint of morbidity and even mortality. Furthermore, in patients with malignant pericardial effusion, histologic examination of pericardial tissue obtained by surgical biopsy was reported to have a low positive yield between 27[11] and 54%.[12] This low yield was explained by the fact that the malignant invasion of the pericardium may be scattered and not seen by random biopsy, especially when the specimen of the visceral layer is not included. Cytologic diagnosis of malignant pericardial effusion may provide an alternative approach to histologic diagnosis. The frequency of malignant cells obtained by cytologic examination of pericardial fluid as reported by various investigators is presented in Table IV. We could specify the tumor type in 24 patients, with adenocarcinoma being most frequent (47%). These findings are similar to those reported by other investigators.[7,8] Because the true number of patients with malignant pericardial involvement is not known, the overall sensitivity cannot be determined. Using the pericardial histology as a gold standard, the sensitivity of the cytologic findings was 78%. In 2 patients, the cytologic findings were falsely negative. False-negative cytologic diagnoses do occur[5,7–12]; therefore, a benign cytologic finding does not exclude malignant pericardial effusion. Of the 3 patients with histologic nonmalignant findings, 2 had cytologic findings that revealed malignant cells. We believe that these malignant cells represent true-positive cytologic findings, whereas the benign histologic findings of the pericardial biopsies represent nonmalignant tissue samples. The development of symptomatic pericardial disease in a cancer patient does not necessarily denote malignancy[3,9, 4,15] and may represent a benign treatable disease. Fraser et al[9] reported that up to 50% of patients with symptomatic pericardial disease and extracardiac neoplasm may have nonmalignant pericardial disease, including delayed radiotherapy-induced pericardial disease, cardiotoxicity induced by drugs such as anthracycline, infections such as tuberculosis and viral pericardial effusion, and autoimmune disorder, as well as idiopathic pericarditis. In the present study, of the 18 patients with benign cytologic findings, only 4 had histologic diagnosis (2 histologically benign and 2 malignant). Two of the other 14 patients had purulent staphylococcal pericardial effusion. Three women with serous pericardial effusion, who had previously received radiation >4,000 rad for breast cancer to the heart region and had survived >14 months, probably had delayed radiation-induced pericardial disease. In the remaining 9 patients, we could not establish the underlying cause for the pericardial effusion (whether benign or malignant), probably allowing for some cases of false-negative cases.

In conclusion, cytologic analysis of pericardial fluid in patients with extracardiac malignancy is an accurate method to distinguish malignant from benign pericardial effusion. This procedure surpasses pericardial biopsies, in view of the lesser danger and better tolerance by the patient, in the evaluation of suspected malignant pericardial effusion and may aid in identifying a previously unsuspected neoplasm.

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Lipoprotein (a) is Not a Risk Factor for Restenosis After Percutaneous Transluminal Coronary Angioplasty

Qiu et al[1] showed that lipoprotein (a) (LP[a]) levels are not increased in unstable angina pectoris, myocardial infarction and after thrombolytic therapy, although there is substantial evidence that LP(a) is a genetically influenced independent risk factor for coronary heart disease.[2,3] LP(a) is present in atherosclerotic plaques and is deposited in vein grafts after coronary bypass surgery.[4] Moreover, LP(a) concentration in serum is a predictor of vein graft occlusion after bypass surgery.[5,6] Whether LP(a) is a prognostic factor for restenosis after percutaneous transluminal coronary angioplasty (PTCA), which represents the main problem limiting the long-term efficacy of this procedure, is not yet known. The frequency of restenosis 3 to 4 months after PTCA is approximately 25 to 35%.[7] Therefore, we studied LP(a) serum concentrations in a series of 65 men (mean age 55 years, range 38 to 70) with coronary heart disease and successful PTCA. LP(a) was measured by Laurell electrophoresis (ready-to-use agar gel, Immuno, Vienna, Austria). Follow-up coronary angiography was performed 12 months after PTCA. LP(a) values were determined 12 months after this angiography. Restenosis was defined as >25% decrease of the initial result and >50% stenosis of the vessel diameter. Thirty-four patients had restenosis (mean age ± standard deviation 56 ± 8 years) and 31 did not (55 ± 9 years).

Both groups did not differ significantly in medical history (smoking habits, hypertension and family history), routine lipid profile (total cholesterol, high- and low-density lipoprotein cholesterols, triglycerides, and apolipoproteins A1 and B) or fibrinogen levels. LP(a) values were 23 ± 28 mg/dl (mean ± standard deviation) in patients with restenosis, and 20 ± 26 mg/dl in those without (p = not significant). Elevated LP(a) levels >20 mg/dl were found in 13 of 34 patients with restenosis and in 10 of 31 without.

Although LP(a) is a proven risk factor for coronary heart disease and reocclusion after coronary bypass surgery, our observations indicate that LP(a) serum concentration does not correlate with risk for restenosis after PTCA.

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Thallium Stress Tests in Asymptomatic Diabetics

Langer et al's[1] May 15, 1991, article in the *Journal* adds to the growing number of reports on silent myocardial ischemia in adults with diabetes mellitus. I disagree with 1 of their conclusions. They state: "Although coronary angiography was not performed in our subjects, previous studies have shown that thallium scintigraphy identified 97% of asymptomatic subjects with abnormal electrocardiograms correctly regarding the presence or absence of coronary artery disease." They reference a study that looked at asymptomatic air crew members with computer-enhanced thallium-201 scintigraphy.[2] Those patients are not comparable to their subjects. The patients in Langer et al's study had normal 12-lead electrocardiograms. There is a big difference. One cannot assume that Langer et al's subjects with abnormal thallium images had significant coronary artery disease.

There are 7 other published studies describing asymptomatic adults with diabetes mellitus and the presence of myocardial ischemia.[3-9] One study used both exercise thallium imaging and coronary arteriography.[9] One hundred thirty-six asymptomatic adults with diabetes mellitus were screened for the presence of coronary artery disease. These patients had no clinical or electrocardiographic evidence of heart disease; 39 had either an abnormal exercise electrocardiogram or postexertional thallium image, or both, and 33 underwent cardiac catheterization with coronary arteriography. Sixty percent of the patients with an abnormal postexertional thallium image had no significant coronary artery disease as defined by coronary arteriography.

Noninvasive tests for detecting the presence of coronary artery disease are not 100% specific. The relatively low prevalence of coronary artery disease in asymptomatic patients results in low positive predic-

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Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

tive values (true positive tests divided by true and false positive tests). I remain unconvinced that Langer et al's subjects who had abnormal thallium studies do indeed have significant coronary artery disease, as would be defined by coronary angiography.

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19 August 1991

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Seismocardiography is Not a New Term

The expression seismocardiography (recording of "the shaking caused by the heart") was established in the 1960s,[1] thus replacing the term ballistocardiography (recording of "the heart's sling shot"). Therefore, seismocardiography should not be considered as a new noninvasive test.[2] In fact, low-frequency vibrations of the chest recorded by different techniques present similar patterns. This holds true not only for seismocardiography, but also for kinetocardiography, which we have used in the past[3,4] by building a simplified but quite accurate homemade mechanical device.

It is worth mentioning that after several decades,[5] the low-frequency vibrations of the chest transmitted from the heart are now the subject of new investigations in ischemic heart disease. During the time when seismocardiography was developed it represented a significant step forward in recording the filling diastolic waves, thus documenting graphically the S3 and S4 sounds. In fact, the first and second velocity filling waves (E and A), the counterparts of S3 and S4 recorded by Doppler echocardiography, reflect left ventricular filling patterns comparable to parameters obtained from radionuclide studies. Figure 1 in Salerno et al's[2] report represents an illustrative example of a seismocardiogram where the peak velocities of the transmitral flow during early and late diastole (atrial systole) are well-recorded. However, in Figure 3, the second filling wave is less prominent, indicating significant variations in its amplitude (recording number 4 from top). Such changes are frequently seen during recording, but in Salerno et al's study, the control group is aged 28 ± 5 vs 63 ± 10 years for the patients with coronary artery disease. At this relatively young age of 28, the S4 is barely recordable. Therefore, one must conclude that the study was unsuccessful in properly matching the age of the control subjects with that of the patients.

While paying due attention to the clinical value of the older techniques, such as seismocardiography, one must recognize that we have never been able to quantify our findings. Quantification is now made possible through the newer techniques, even though many problems remain to be solved.

William Dock, a recognized pioneer in the field of ballistocardiography (seismocardiography, as he called it), told me several years ago, not too long before his passing, that he envies me, his former long-time associate, for the opportunity we now have to study the heart by new and more reliable techniques.

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25 July 1991

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REPLY: We wish to thank Dr. Zoneraich for pointing out that the word "seismocardiography" is not new. We were aware that the term has existed for some time, being defined in Dorland's Illustrated Medical Dictionary as "the selective recording of cardiac vibrations."[1] We had previously found several papers on seismocardiography in the Russian literature.[2,3] Apparently, this method has been studied in the Soviet Union for several decades, even before Dock and Zoneraich,[4] in which seismocardiography is described in a footnote to their case report as a "record of the shaking caused by the heart." We were not aware of their report; it may be the source of the term for Dorland. (The lexicographers at the offices of the dictionary were unable to provide us with their original source!)

As we discussed in our paper on seismocardiography,[5] the technique is derived from earlier forms of displacement cardiography including kinetocardiography, ballistocardiography (as mentioned by Dr. Zoneraich in his letter) and, more recently, cardiokymography. The modern seismocardiograph includes considerable technological advancements that were not available in the 1960s. These include improved sensor technology (an ultrasensitive but accurate piezoelectric accelerometer), optimized accelerometer placement, analog-digital conversion, a microprocessor for digital signal-processing and automated wave analysis, and neural network technology for computerized interpretation.[5-7] We believe the technique in its current form is "new," because these technical changes result in markedly enhanced diagnostic power.

We agree that the control group in our study of seismocardiography during angioplasty is younger than the experimental group. We did not detect any baseline differences between the recordings of the 2 groups that would have enabled us to identify the control subjects during the blinded analysis. We used only changes from baseline to identify the patients with angioplasty and, thus, think that this is a minor issue in the report.

We agree with Dr. Zoneraich that the seismocardiogram is sensitive to diastolic filling. One of the examples in our paper illustrates this. Although in normal subjects, small variations in the amplitudes of the RF (related to early diastolic filling of the ventricle) and AS (related to atrial systole) waves are seen, these small variations are increased substantially in patients during ischemia.[5,8] With quantitative seismocardiography it is now possible to define the normal range for the RF- and AS-wave amplitudes, and to identify patients with amplitudes outside the normal range. This opens the possibility of using the technique as a noninvasive measure of ventricular filling pressure at rest, as well as during various interventions. This may enable the technique to be used to evaluate response to treatment for heart failure and to evaluate patients with symptoms possibly related to myocardial ischemia or heart failure.

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Single Inoue Balloon Catheter Versus Double Mansfield Balloon Catheter Techniques in Percutaneous Balloon Mitral Valvuloplasty

It was extremely gratifying to read the recent report by the group from Riyadh, Saudi Arabia[1] —that both the single Inoue balloon catheter and double Mansfield balloon catheter techniques for percutaneous balloon mitral valvuloplasty achieved similar mitral valve areas. This study assumes considerable significance, because these investigators were the pioneers in introducing the double balloon technique of percutaneous balloon mitral valvuloplasty.[2] Moreover, their study was the first of its kind on patients with comparable mitral valve and subvalvular pathology. As they pointed out, all the previous published series included noncomparable groups of patients, with different ages and mitral valve and subvalvular anatomy. Therefore, this report settled once and for all the ongoing dispute concerning the relative virtues of these 2 commonly employed techniques of percutaneous balloon mitral valvuloplasty.

One significant added advantage of the Inoue balloon catheter technique over the double Mansfield balloon technique is the considerably shorter procedure time. This assumes an even greater significance when one deals with seriously ill patients or female patients in their reproductive years in whom irradiation should be kept at a minimum.

The chief disadvantage of the Inoue balloon catheter technique is, as I[3] and these authors pointed out, is the expense. Hopefully this will be overcome if and when a reusable Inoue balloon catheter becomes available.

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Washington, D.C.
9 September 1991

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Correction

Rationale and Design of a Secondary Prevention Trial of Lowering Normal Plasma Cholesterol Levels After Acute Myocardial Infarction: The Cholesterol and Recurrent Events Trial (CARE) (December 1, 1991: 1436–1446). On page 1446, the chairman of the Publications Committee of the CARE trial is Jean-Lucien Rouleau, University of Sherbrooke, Quebec, not Jacques Rouleau, as printed.

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INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values that resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without c ing their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a s neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is i to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diu therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. Th bility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing s intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of qui should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase seru potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, tria terene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used wi caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL re the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tabl This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesiu

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomit lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum li levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by qui coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node h ngiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: in vitro mammalian cell mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, in vitro chromosome aberrat with V79 cultured lung cells, and in an in vivo cytogenetic study with rat bone marrow. There were no adverse effects on ferti reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg a mg/m^2, respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in hu milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat co to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controll uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cann ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patient participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in more than 1400 patients treated 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-co hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular acc hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea ni were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of once-daily dosing interval. In such patients, an increase in dosage or twice-dai administration may be warranted.

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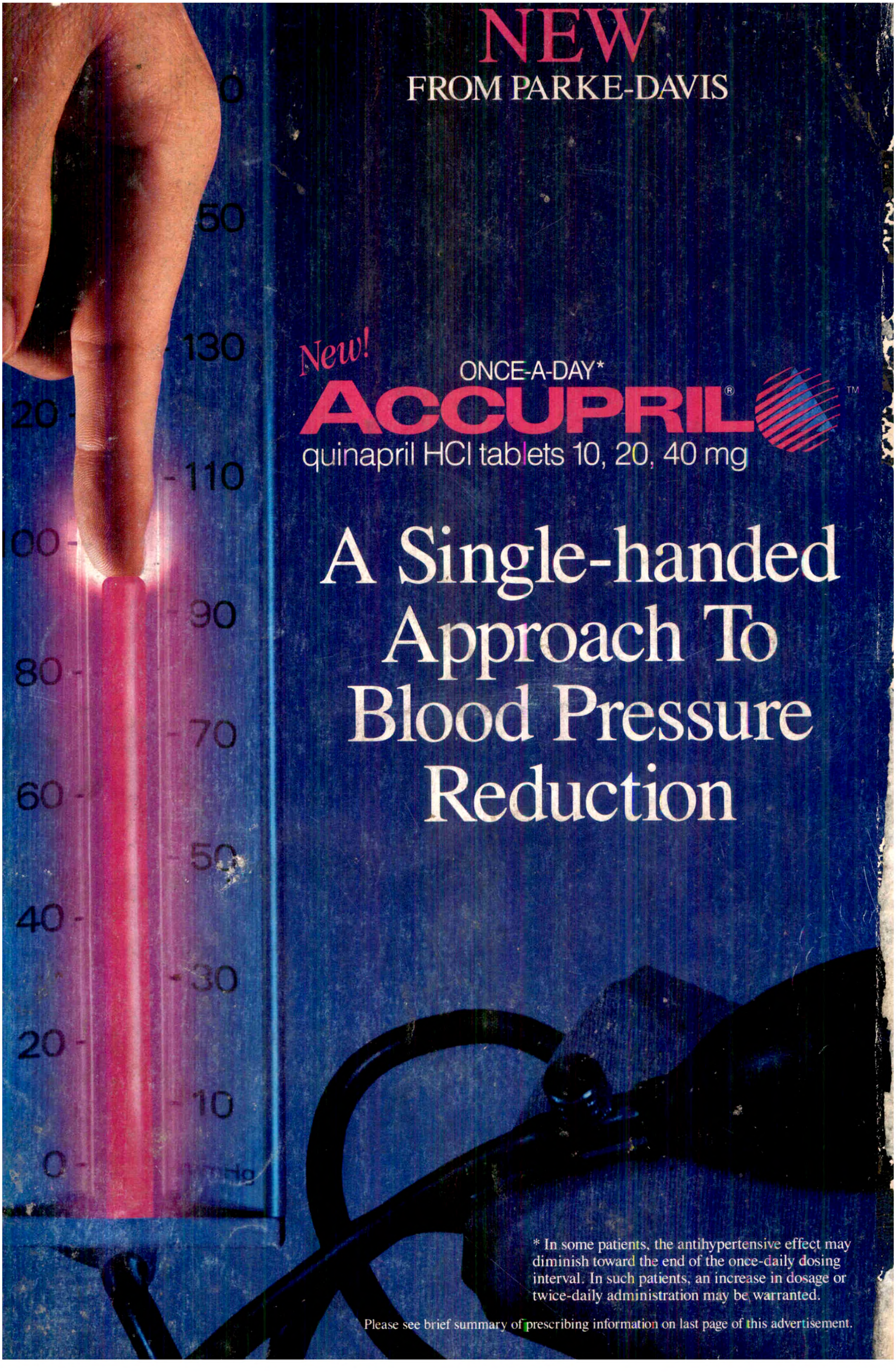

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Approach To
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Reduction

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Please see brief summary of prescribing information on last page of this advertisement.